The American Journal of Medicine

Symposium on Drug Addiction

Nathan B. Eddy, M.D.
Guest Editor



May 1953

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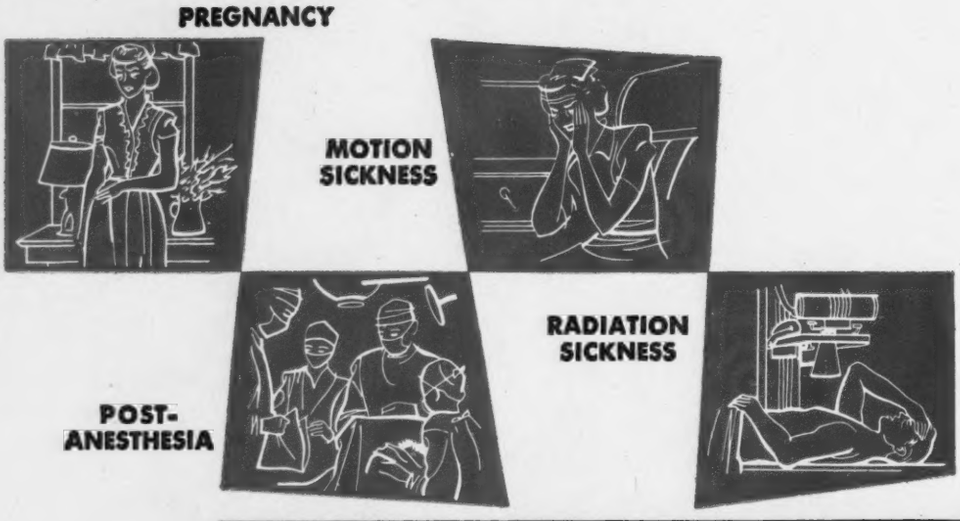
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History and Mechanism of International and National Control of Drugs of Addiction Alfred Tennyson 578

Drug addiction, while not the ubiquitous menace indicated in sensational news accounts, is nevertheless a widespread, serious and growing problem which all responsible physicians should recognize. The Guest Editor of the current symposium on this topic, Dr. Nathan B. Eddy, himself a life-long student of narcotic drugs and drug addiction, divided the over-all problem into seven major categories. To cover each subdivision he has obtained the contribution of an outstanding authority in the field. The result is a concise, up-to-date, informative and authoritative survey of the characteristics of addictive drugs and drug addiction.

Contents continued on page 5



in headache

prompt...prolonged...prescribed pain relief

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Reviews

Psychomedical Survey of a Private Outpatient Clinic in a University Hospital
BERNARD I. LEWIS 586

It is generally appreciated, in a vague way, that perhaps one- to two-thirds of patients seen these days in private or clinic practice have little if any "somatic" disease and suffer chiefly from "psychic" disorders. To obtain more precise data, Dr. Lewis has made a penetrating analysis of 163 patients who applied to the Private Outpatient Service of the Johns Hopkins Hospital and, being an internist himself, presents the results in lucid, direct language that the internist will appreciate. Dr. Lewis estimates that about 25 per cent of these patients had significant "somatic" disease alone, 50 per cent had "psychogenic" disorders alone and about 25 per cent had significant degrees of disturbance in both categories. In about two-thirds of the cases with "psychogenic" problems, sympathetic and patient treatment by the non-psychiatric physician, it was thought, would suffice. There is indeed "urgent need of general reorientation of medical attitudes and perspectives."

The Phenobarbital Sensitivity Syndrome
THOMAS E. MCGEACHY AND WILLIAM E. BLOOMER 600

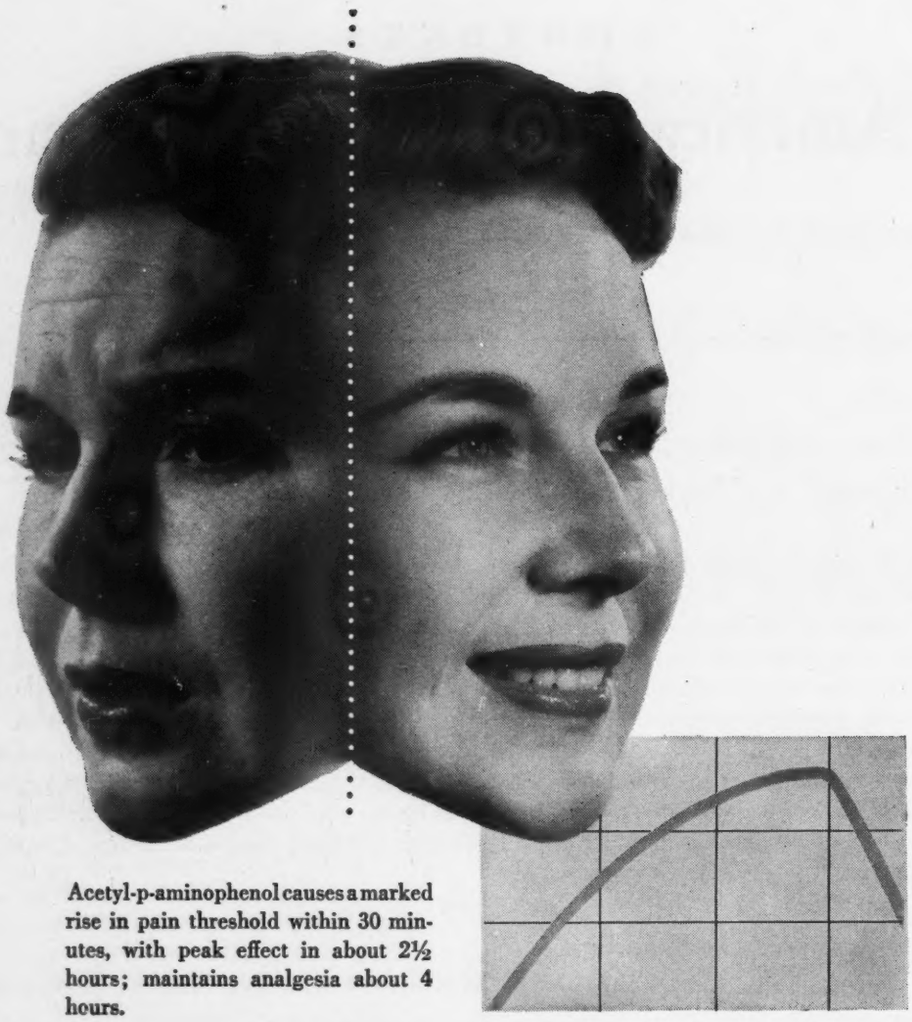
Three cases, two of them fatal, are described to illustrate occasional phenobarbital idiosyncrasy characterized by acute fever, delirium, exfoliative dermatitis and diffuse damage to the liver, kidneys and other organs.

Seminars on Blood Coagulation

Allergic Purpura, Including Purpura Due to Foods, Drugs and Infections
J. F. ACKROYD 605

After classifying the allergic purpuras into those associated with an erythematous exanthem (Henoch-Schönlein syndrome) and the true purpuras (without associated exanthem) due to infections or drugs, Dr. Ackroyd goes on to consider the fundamental nature of the purpuric lesion which he concludes primarily reflects a lesion of the capillary endothelium; thrombocytopenia, which need not be present, merely exaggerates the tendency to hemorrhage. The two phenomena represent different aspects of a common antibody response. Dr. Ackroyd then gives full descriptions of the Henoch-Schönlein syndrome, of purpuras associated with infections, and of his own immunologic studies of the thrombocytopenic purpura occurring in subjects sensitized to sedormid. The whole represents an outstanding contribution to this subject.

Contents continued on page 7



Acetyl-p-aminophenol causes a marked rise in pain threshold within 30 minutes, with peak effect in about 2½ hours; maintains analgesia about 4 hours.

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SQUIBB

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Case Reports

Methamphetamine Intoxication W. GORDON WALKER AND JOHN COLLINS HARVEY 633

The clinical picture in this case was puzzling, at first suggesting an infectious encephalitis. Subsequent developments suggest that methamphetamine intoxication was the cause, and since this drug is widely employed the experience is worth noting.

A Metabolic Study Following Extensive Resection of the Small Intestine for Sarcoma HERTA SPENCER, ISAAC LEWIN AND DANIEL LASZLO 636

Very few metabolic studies dealing with the effects of extensive small bowel resection, a more common procedure now than hitherto, are available. The report therefore is of unusual interest, particularly since it is shown that remarkable adjustment to loss of absorbing surface can be made.

Acute Idiopathic Bulbar Encephalomyelitis . . . MAJOR STUART H. WALKER 642

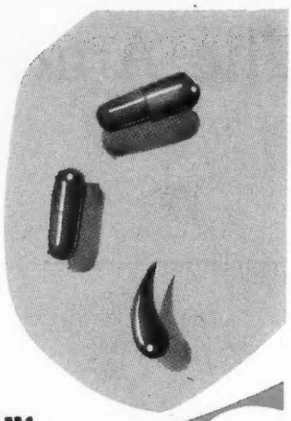
A lucid discussion of acute idiopathic bulbar encephalomyelitis, with two illustrative case reports, and differential diagnosis in respect particularly to the viral encephalomyelitides and brain stem neoplasia.

Paradoxic Embolism. . . . . NOLTON H. BIGELOW 648

Much is heard but little is seen of paradoxic embolism. Here is an authentic case.

Advertising Index on 3rd Cover

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1. Pollak, O. J.: Delaware State M. J. *24*:157, 1952.
2. Zelman, S.: Arch. Int. Med. *90*:141, 1952.

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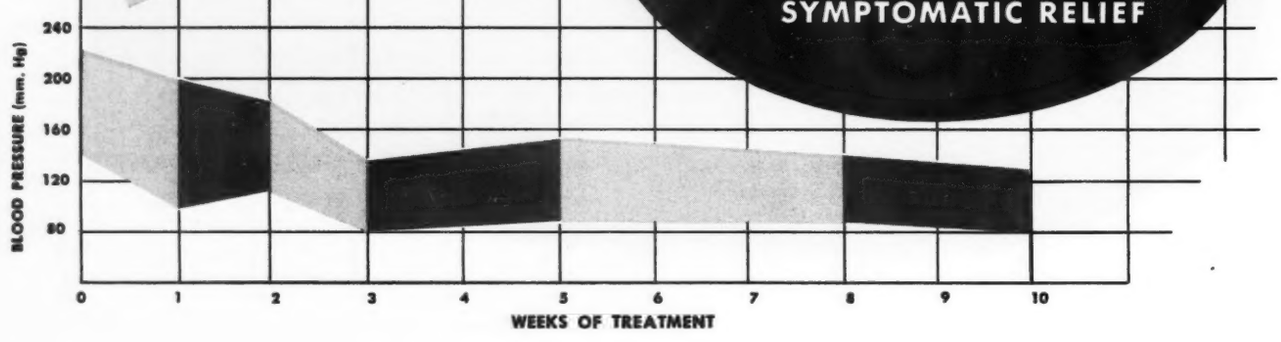
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MARKED DYSPNEA...
TRANSIENT HEMIPLEGIA

BLOOD PRESSURE REDUCED WITH VERILOID TO

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RESULT:
VIRTUALLY COMPLETE
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*Kauntze, R., and Trounce, J.: Treatment of Arterial Hypertension with Veriloid, Lancet 2:1002 (Dec. 1) 1951.
**Page, I. H.: Arterial Hypertension, Pennsylvania M. J. 55:737 (Aug.) 1952.

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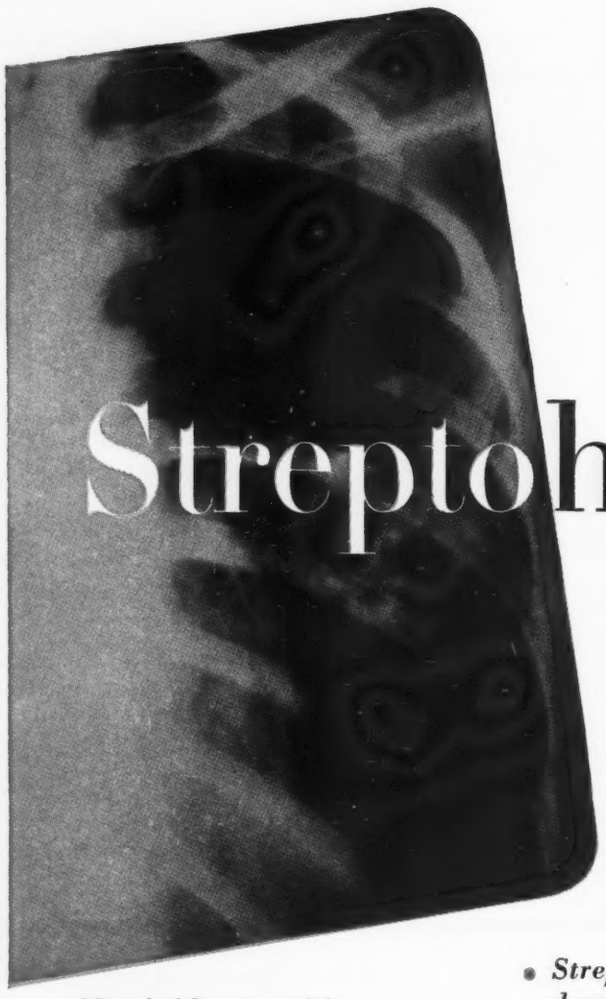
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(Sciatic—Intercostal—Facial)

"...patients responded with complete relief of pain"*

WITH PROTAMIDE

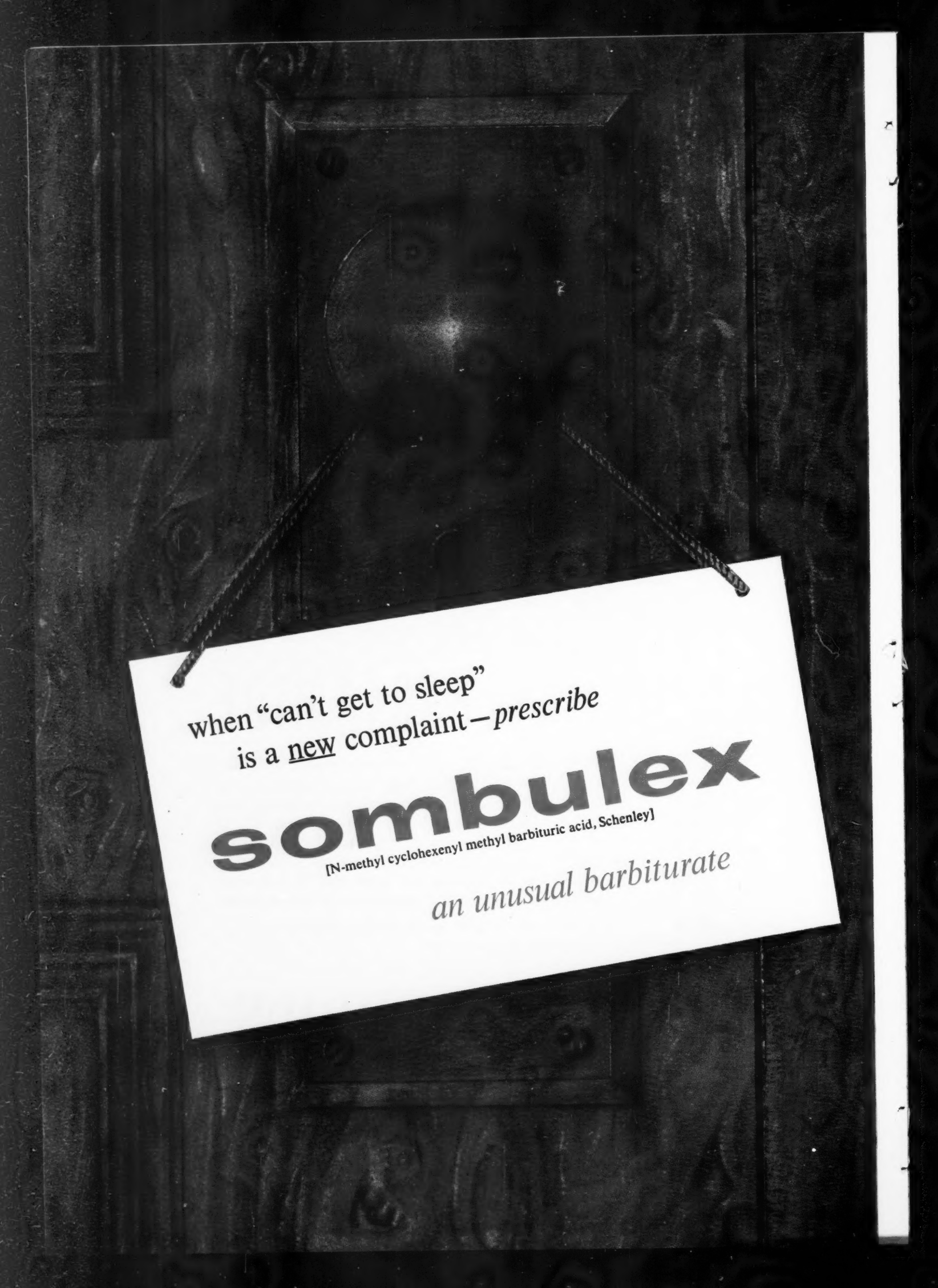


Richard T. Smith, M.D., in a currently published paper, "Treatment of Neuritis with Protamide" reports: 84 patients of 104 had complete relief of pain in sciatic, intercostal and facial neuritis with one daily injection of Protamide for five or ten days. "... 49 were discharged as cured after five days of therapy." No intolerance to Protamide, systemic or local was found in the 125 patients (104 plus 21 controls). Two qualifications for practical application of this study are:

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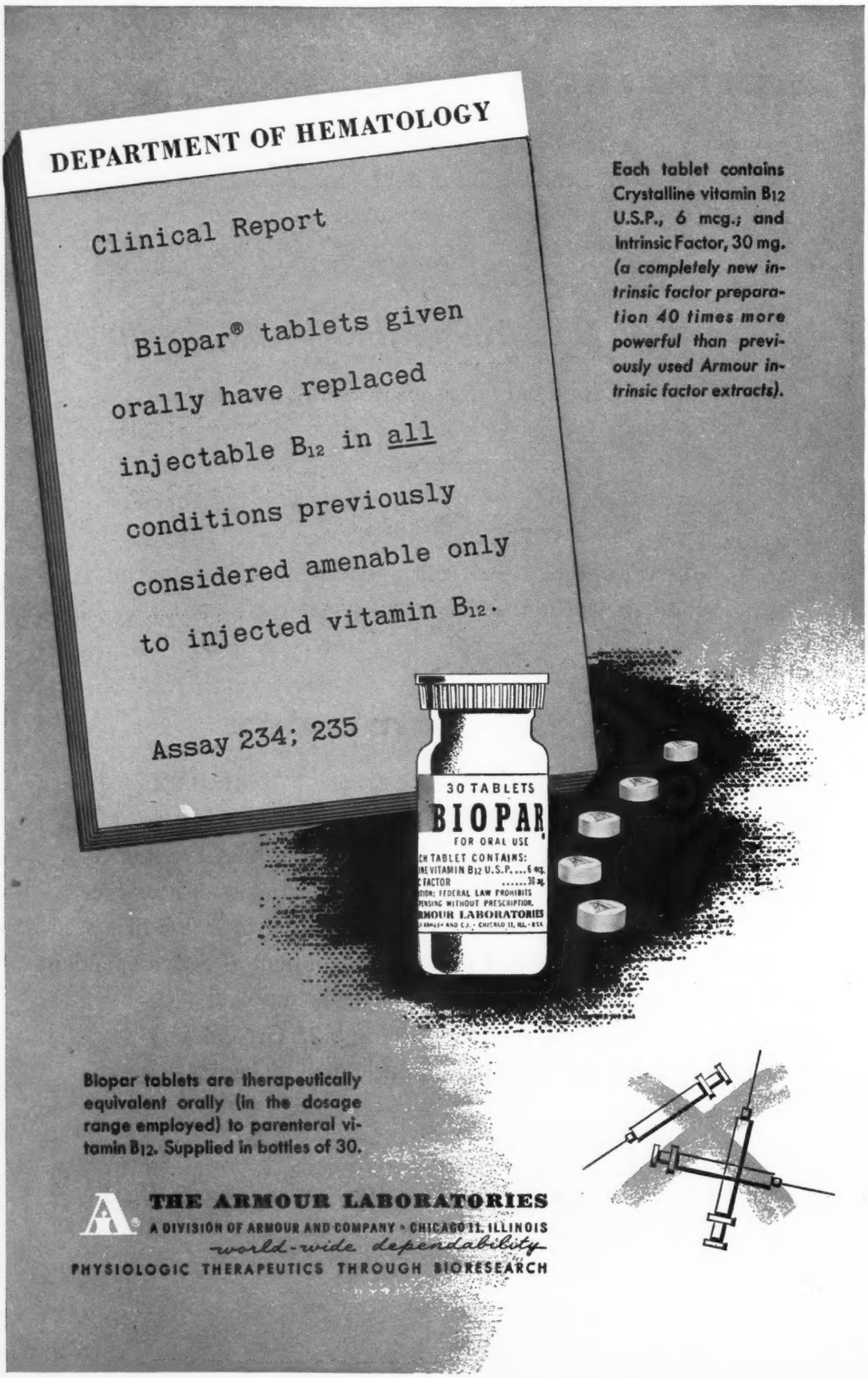
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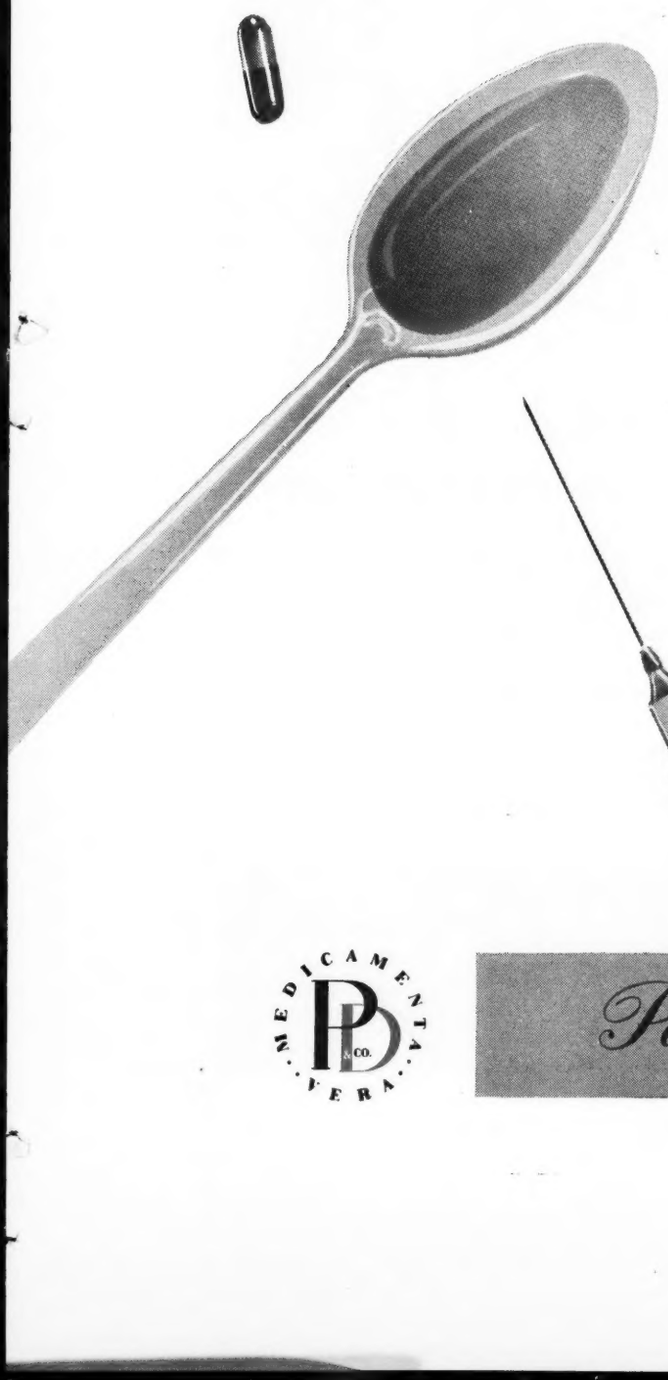
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Clinical Report
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Greaseless, long-lasting SKIN PROTECTION

for industrial dermatoses and contact allergies

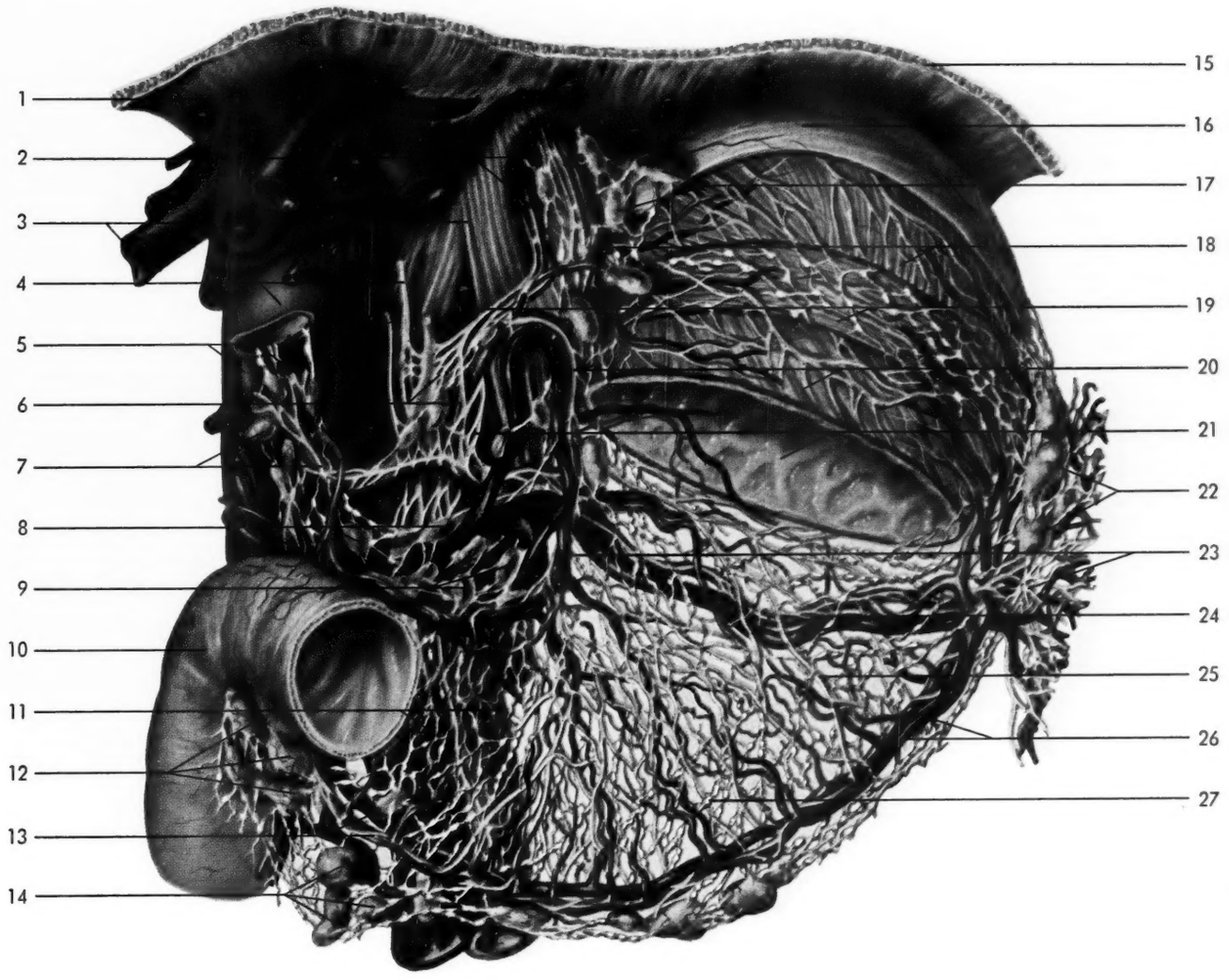
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Anatomy *of the* Stomach



1 Middle and left hepatic veins

2 Right vagus nerve and esophagus

3 Right hepatic vein and crura of diaphragm

4 Inferior vena cava and greater splanchnic nerve

5 Portal vein and hepatic artery

6 Celiac plexus and celiac artery

7 Hepatic lymph node and hepatic rami of vagus nerve

8 Gastroduodenal artery and suprapyloric lymph nodes

9 Superior gastric lymph nodes

10 Duodenum

11 Superior mesenteric artery and vein

12 Subpyloric lymph nodes

13 Right gastroepiploic artery and vein

14 Inferior gastric lymph nodes

15 Diaphragm

16 Serosa

17 Paracardial lymph nodes

18 Left vagus nerve and longitudinal muscular layer

19 Abdominal aorta and circular muscular layer

20 Left gastric artery and oblique muscular layer

21 Celiac rami of vagus nerve and gastric mucosa

22 Splenic lymph nodes

23 Left gastric (coronary) vein and splenic rami of vagus nerve

24 Splenic artery and vein

25 Gastric rami of vagus nerve

26 Left gastroepiploic artery and vein

27 Gastric lymphatic plexus

This is one of a series of paintings for Lederle by Paul Peck, illustrating the anatomy of various organs and tissues of the body which are frequently attacked by infection, where aureomycin may prove useful.

Lederle

In perforated viscus,

in elective surgery of the stomach,

as well as for

gastroenteric infections–

Aureomycin

HYDROCHLORIDE CRYSTALLINE

often acts promptly to prevent

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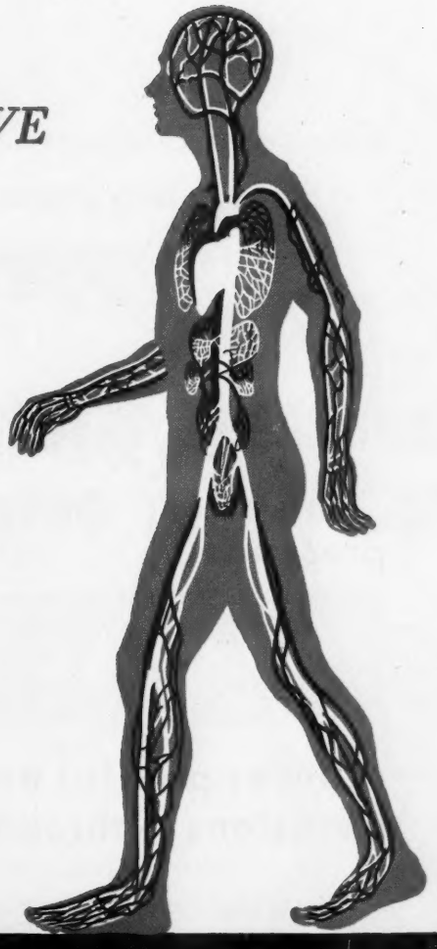
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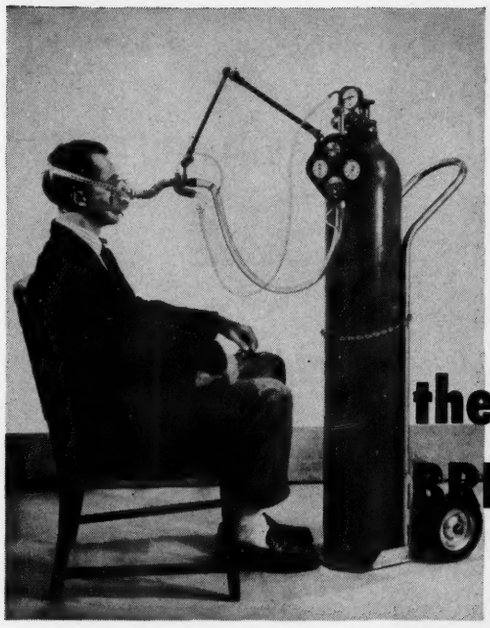
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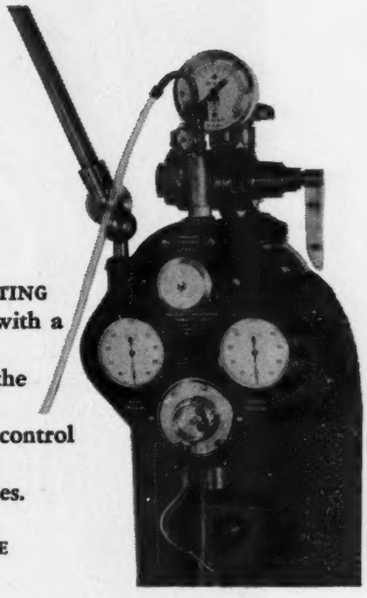
[1]*Bargen, J. A., and Jackman, R. J., Journal Lancet, 72:11, Nov., 1952.*

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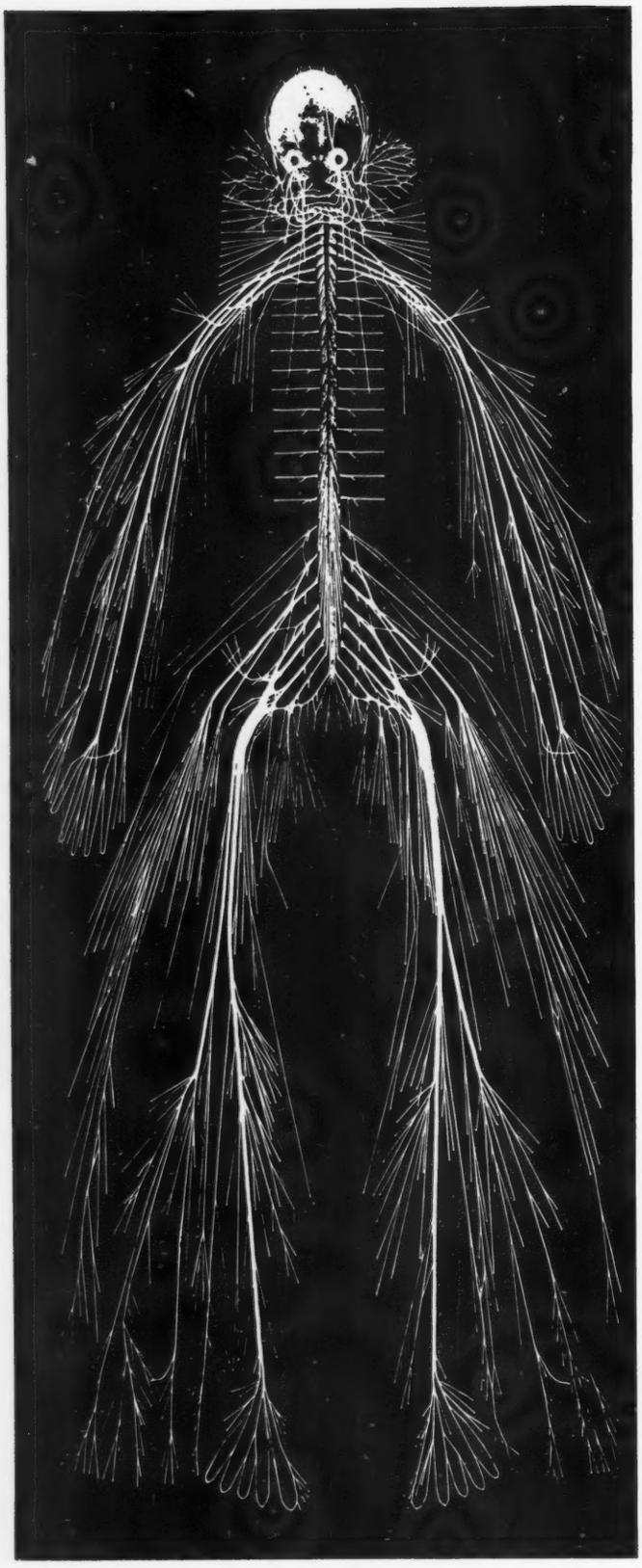
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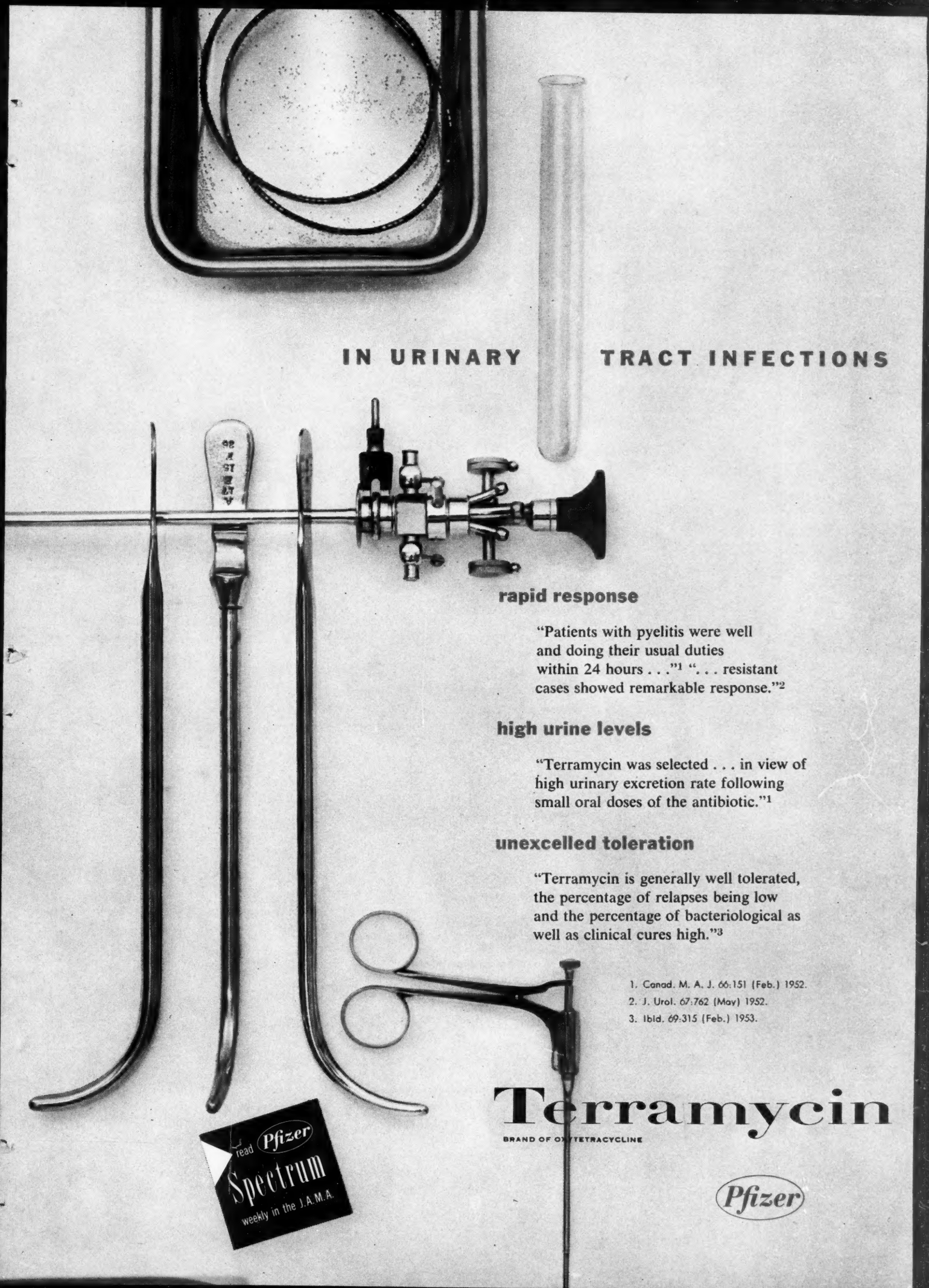
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← Dissection of nervous system by R. P. Weaver, A.M., M.D., Sc.D., late Professor of Anatomy, Hahnemnan Medical College and Hospital. Courtesy of Hahnemann Medical College Museum.



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1. Canad. M. A. J. 66:151 (Feb.) 1952.
2. J. Urol. 67:762 (May) 1952.
3. Ibid. 69:315 (Feb.) 1953.

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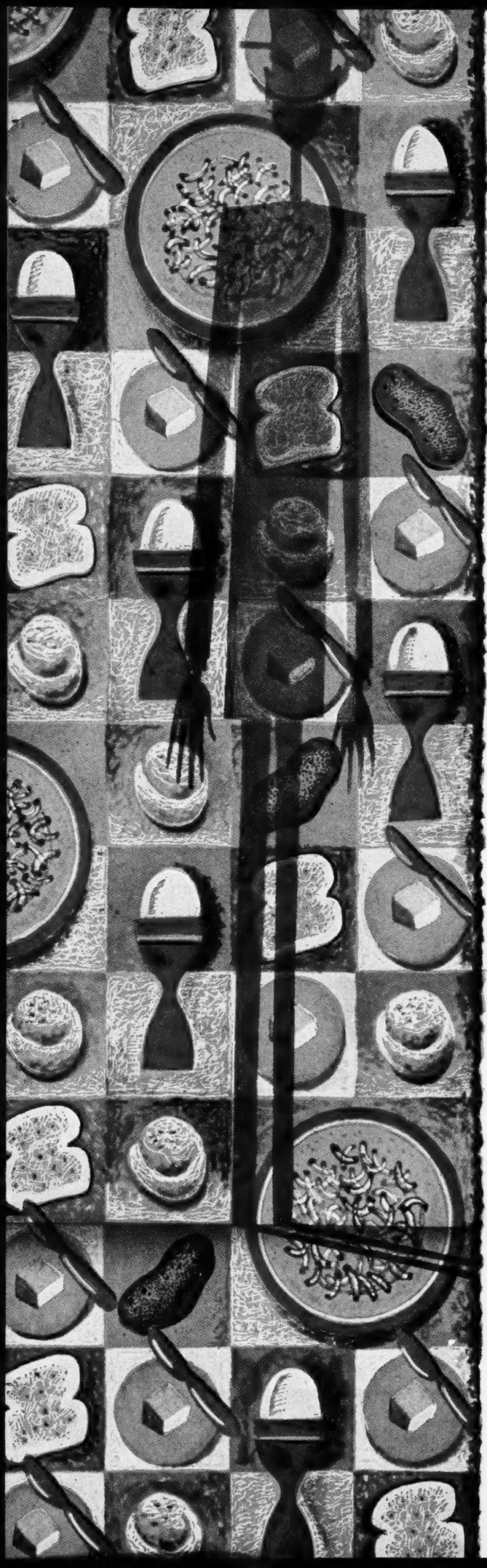
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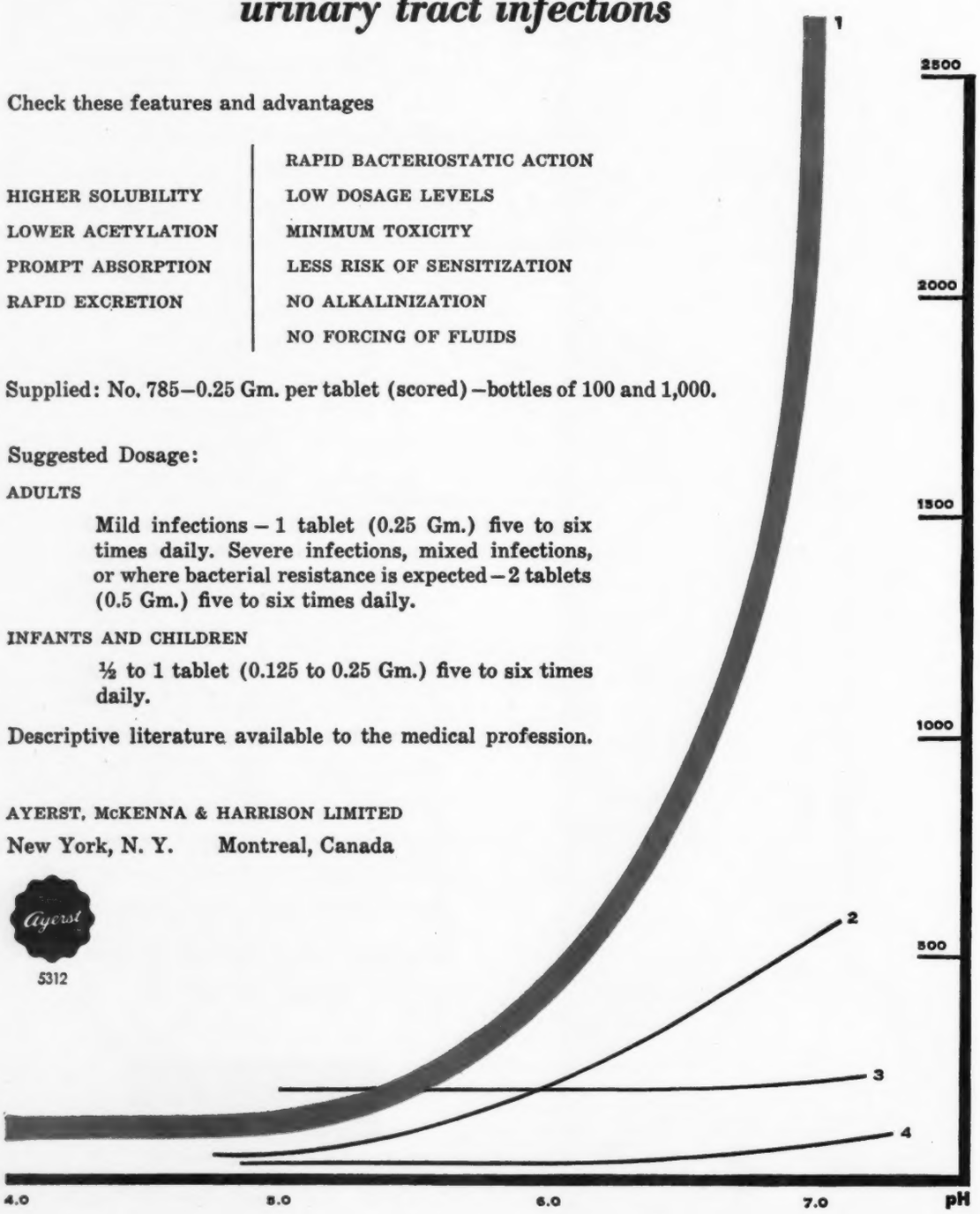
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Snow, W. B., and Coss, J. A., N. Y. State J. Med. *52: 319, Feb. 1, 1952*

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1. Slinger, W. N., and Hubbard, D. M. (1951), Arch. Dermat. & Syph., 64:41, July. 2. Slepyan, A. H. (1952), Ibid., *65:228, February. 3. Ruch, D. M. (1951), Communication to Abbott Laboratories. 4. Sauer, G. C. (1952), J. Missouri M. A. 49:911, November.*

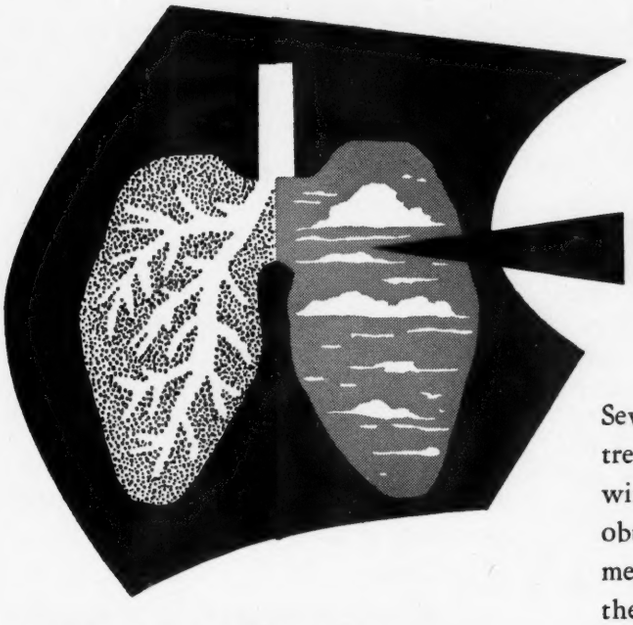
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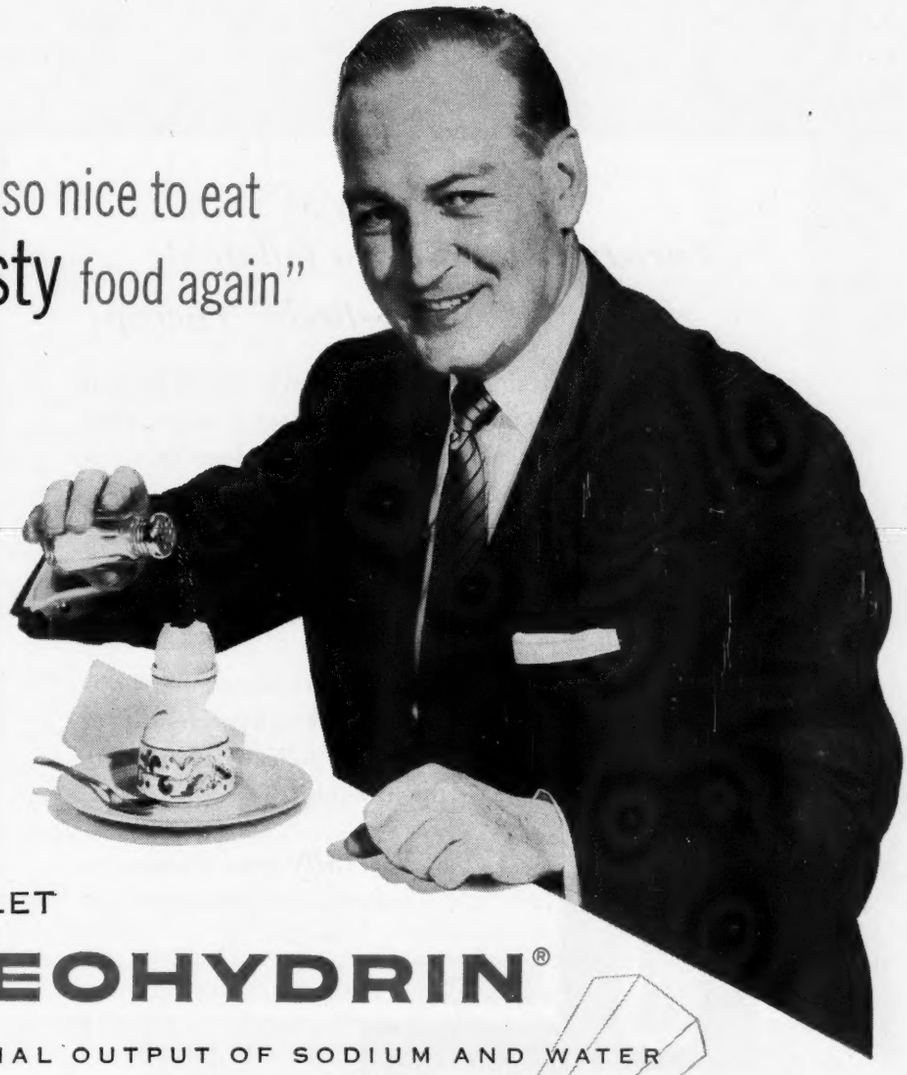
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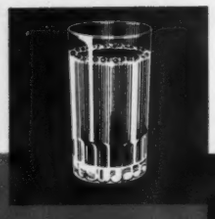
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The American Journal of Medicine

Vol. XIV MAY, 1953 No. 5

Foreword

THE many investigations of the past two years indicate an upward trend in drug addiction, and that the increase is predominantly among the younger members of urban populations is reflected in the records of the U. S. Public Health Service Hospital for the treatment of drug addiction at Lexington, Kentucky. The average age of admissions to the hospital has dropped ten years, and for a time teenagers and young adults were being admitted at the rate of fifteen to twenty a day. However, the drug addiction situation is not as bad as some sensational stories would indicate nor, on the other hand, is it as innocuous as a recent magazine article (Harper's Magazine, February 1952) asserts. Informed sources now are of the opinion that the crest of the wave has passed and that increased facilities for vigorous law enforcement are bringing about a downward trend.

No one can say with definiteness how many addicts there are today in the United States (one conservative estimate is 1 in 3,000 of our population); but whatever the figure, an established addiction is like a contagious disease and the more our attitude toward and handling of addiction approximates our attitude toward and handling of recognized contagious diseases the better will be our understanding and control of addiction. Physicians can do much to foster this attitude and handling by keeping themselves thoroughly informed of the characteristics and recognition of addictions, including addiction to the barbiturates and to the new potent analgesics, all of which unfortunately have shown addiction liability and some of which already have appeared in illegitimate narcotic traffic. Physicians can help, too, by an informed attitude toward the handling of an addict* and by their constant urging of local facilities for the treatment of addiction. Physicians cannot supply drugs to addicts simply to maintain their addiction and the advocated establishment of government clinics for the purpose has been tried and failed. Adequate quarantine and institutional treatment is the best line of attack and this means not only treatment during the acute phase of withdrawal but, even more importantly, prolonged rehabilitative treatment directed toward adjustment of the individual to his environment so that he does not have to seek escape again with drugs.

Because of the physician's role in the battle against addiction your Editor has arranged the present Symposium. The subjects have been selected for wide coverage of all angles and the authors in each instance are individuals with long contact and investigative experience with that aspect of the problem to which he has contributed in this symposium. Throughout, attention is given not only to morphine and its derivatives and the other potent analgesics but also to other potentially addicting substances, barbiturates, cocaine, marihuana, etc., excluding only alcohol on account of space limitations. Addiction is no longer a problem simply of the opiates. The new synthetic analgesics are raising problems and difficulties of their own and the rising abuse of the barbiturates is of the greatest importance. Each of the authors has been impressed with the need for this wide coverage and each has labored to attain it although it has made his task much more difficult. The Editor takes this opportunity to express his appreciation of the cooperative effort of all of the authors.

NATHAN B. EDDY, M.D.
Chief, Section on Analgesics, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

* Report to the Council. What to do with a drug addict. *J. A. M. A.*, 149: 1220–1223, 1952.

Symposium on Drug Addiction

The Drug Addiction Problem*

JOSEPH M. BOBBITT, PH.D.

Bethesda, Maryland

In 1951 there was a great deal of publicity over what appeared to be an increase in drug addiction among minors. Apparently this concern developed in part as a consequence of an increase in the admission rates at the U. S. Public Health Service Hospital, Lexington, Kentucky, among patients under twenty-one years of age. In fact, the rate of admission went up by a very large figure. The number of such persons, however, did not increase to an alarming extent in terms of absolute size. There was a tendency on the part of some persons to extrapolate these data to arrive at the conclusion that the youth of our country were rapidly becoming drug addicts. Such conclusions do not seem now and did not seem then to be justified. First, it was clear that most of the admissions represented young people from New York, Chicago, Washington and a few other large centers of population. Second, an extremely high percentage of these admissions were from minority groups in these large cities. The largest segment was Negro. New York contributed a fair number of Puerto Ricans. Most of the admissions were from relatively depressed areas of the cities involved. At any rate, one could only conclude that there was a fairly large increase in drug addiction among youth in rather definable, socio-economic areas of large cities.

Administrative policies in municipalities could have contributed something to the Lexington statistics aside from any real increase. It is quite possible for drug addiction to be overlooked by juvenile court authorities and the police if they are not looking for this condition. The psychiatrist at the juvenile court in Washington, reported in June, 1951, that he himself failed to recognize drug addiction in a fairly large number of youths whom he had seen prior to the matter's becoming one of public concern. In other words, a year before this date he would have been able to say that he had observed little drug addiction or none. At the time he reported he was able to say that he had observed drug addiction in a fairly large number of individuals. Also, if communities decided that addicts who were recognized should be sent to Lexington and took this step more frequently than had previously been the case, the Lexington statistics would again be affected in terms of an increased admission rate for young people.

One of the factors in the overestimation of the increase in drug addiction among minors was a belief that only a small proportion of those actually addicted were officially known. A study conducted under a National Institute of Mental Health grant to the Chicago Area Project in Chicago tends to show that this belief is a mistaken one. This group used technics of investigation which involved close rapport with known addicts in the Chicago area. They were successful in securing from many such addicts names of other youths known to them to be using drugs. When these listings were compared with official records of youths known to be drug addicts in Chicago, it was shown that the official list contained almost all the names secured from the informers. Therefore, one might conclude with some validity that the official statistics represent, at least in the case of Chicago, a fairly valid estimate of the total problem, not of a small fraction of it.

Since the middle or perhaps the fall of 1951, there has been a tendency to agree that the problem is diminishing. Reports from the National Institute of Mental Health Regional Office consultants are fairly uniform in saying that the communities in their regions believe that the problem is less acute than it was previously. Both New York and Chicago have provided some facilities for the care of narcotic addicts in their own communities. New York opened Riverside Hospital on North Brothers

* From the National Institute of Mental Health, National Institutes of Health, Public Health Service, Federal Security Agency, Bethesda, Md.

Island but it is not filled to capacity. This fact is explained by a staff shortage which is now being overcome. With adequate staff, it is expected that the actual patient population will increase to capacity; but it is believed that the incidence of new cases is not now increasing. Chicago established two outpatient clinics for dealing with young narcotic addicts. One was dedicated primarily to service; the other attempted to perform a kind of research function. In so far as the local facilities were adequate in handling the problem among our youth it could be expected that the Lexington admission rate for this age group would decline, and this is what has happened. The over-all admission rate has not declined appreciably, but some people now conclude that the problem is less because the Lexington youth problem is less. This conclusion is perhaps as misleading as were the conclusions drawn from the earlier increase in the admission rate at Lexington. Obviously if Chicago and New York are not sending all of their addicts or a large percentage of their addicts to Lexington, then Lexington should have fewer addicts.

Other communities have taken some action with respect to the problem. Detroit had a Mayor's Committee on Rehabilitation of the Narcotic Addict in operation for approximately one year. A good job seems to have been done in integrating the efforts of the police department, social agencies, youth agencies, schools and churches of the city. It seems apparent that the committee was successful in producing excellent police work. It is the author's understanding that an outpatient clinic for narcotic addicts was provided for in the budget of the city beginning July 1, 1952. There may be other cities which have taken similar action. Also, the Federal Bureau of Narcotics has secured some additional agents and has, therefore, increased its ability to cope with the drug traffic. Many cities, including Washington, have put increased emphasis on police effort in this field. The point is this: there have been some steps taken by communities to deal with the problem and by the enforcement authorities to decrease the amount of drug traffic. Pretty certainly, however, not enough has been done really to make drugs unavailable to young people or adults. Further, the facilities for treatment and care that have been created are not numerous enough or extensive enough really to have changed the nature of the problem. Therefore, one should be as skeptical about the present assertion that the problem has decreased almost to the vanishing point as one should have been about the original assertions that it was gargantuan. It is probable that there was in fact some increase in the amount of drug addiction among young people in the years 1950 and 1951. It is not likely that anybody knows how large this increase actually was; probably it was overestimated. Also, there may have been some decrease in the last year due to a large variety of factors (public concern, enforcement activities, and treatment and care facilities), but the amount of this decrease is not really known. The present belief that the problem is no longer of prime importance probably represents, therefore, a reaction to some actual decrease plus some re-evaluation of the original data and a realization upon the part of many people that the original increase was somewhat magnified in the public mind.

The problem of drug addiction among young people, as among adults, is a continuing one which has not changed materially in the last two years. However, we have methods for dealing with this problem which have not been adequately utilized, although it is nobody's fault that such is the case. The improvement of all community facilities for dealing with youth, the provision of arrangements, whether they be local or not, for dealing with apprehended addicts, enforcement activities directed toward those in the business of drug sale as contrasted with those who are the victims of the habit and a thorough acceptance of the need to deal with the addict himself as a sick person deserving of treatment and rehabilitation could do much to solve the problem in a basic and continuing way. It is not assumed that the problem can be eliminated.

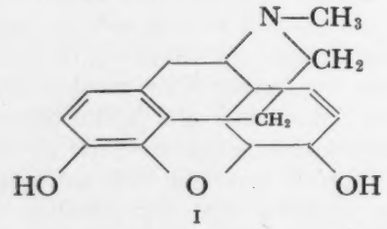
The Chemistry of Drugs of Addiction*

EVERETTE L. MAY, PH.D.
Bethesda, Maryland

SUBSTANCES which have come to be regarded as addiction-producing are very diverse not only with respect to their chemical constitution but their physiologic behavior as well. However, the majority of these substances fall into one of three classifications: (1) morphine and transformation products, (2) synthetic analgesics and (3) sedatives (barbiturates) and hypnotics. A fourth group of miscellaneous substances will be discussed briefly in order to present as complete a picture as possible in a reasonable compass. The first two groups comprise the principal drugs possessing analgesic activity and with one exception, namely, the dithienylbutenes, have several common structural features. The barbiturates bear little or no chemical resemblance to the analgesic drugs but are more closely interrelated than the latter. They have come into prominence in connection with drug addiction† during the last decade. The miscellaneous substances have no particular common denominator chemically but are to some extent related in their excitant action on some functions of the nervous system.

MORPHINE AND TRANSFORMATION PRODUCTS

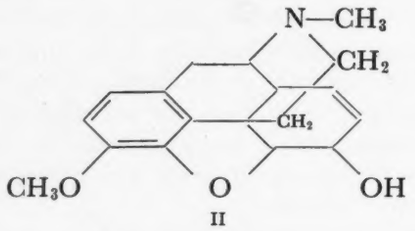
Undoubtedly the best known and most widely used compound of proved addiction liability is the powerful analgesic agent, morphine. The generally accepted structure (I)



I

proposed by Gulland and Robinson[2] in 1925 has been confirmed beyond all reasonable doubt by the total synthesis of morphine recently published by Gates and Tschudi.[3] As is readily seen it is fundamentally a partially hydrogenated phenanthrene containing a fused N-methylethylamine system and bearing one phenolic and one alcoholic hydroxyl group. A third oxygen atom forms a bridge between the terminal rings. Alternatively, morphine may be considered to be a piperidine, an isoquinoline or a benzofuran derivative.

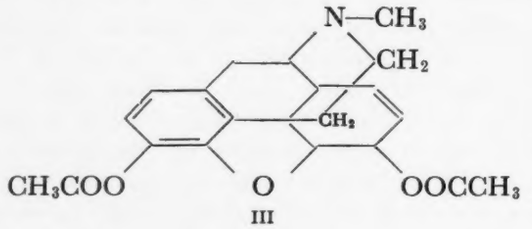
Methylation of the phenolic hydroxyl group of morphine gives codeine (II) (which also occurs



II

in opium) a much weaker analgesic agent which nevertheless has definite addiction liability.[4] Other phenolic ethers of morphine such as the ethyl (dionin®) and benzyl (peronin®) lie between morphine and codeine in their physiologic action.

Upon acetylation of both hydroxyl groups of morphine one obtains heroin (III) a strong,



III

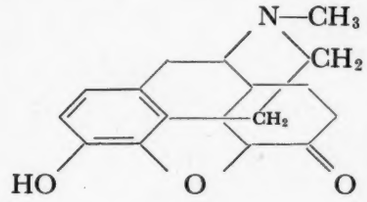
fast-acting drug which rapidly gives rise to addiction. Its potency and ready accessibility by a simple chemical change of morphine make heroin the drug of choice in illicit drug traffic. Qualitatively it is morphine-like in all respects and can do nothing clinically which cannot be accomplished by other drugs less prone to abuse. The manufacture and use of heroin have already been prohibited in many countries including the United States; its worldwide abandonment

† For a definition of drug addiction see reference 1.

* From the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

in medical practice would materially strengthen the forces of narcotics control. Heroin is typical of the derivatives obtained by esterification of the hydroxyl functions of morphine with acids such as propionic, valeric and benzoic.

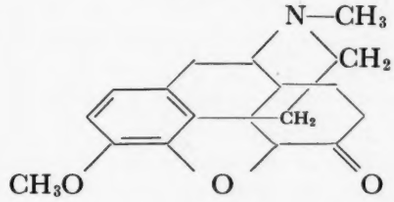
Dilaudid® (dihydromorphinone, IV) results from the rearrangement of morphine under the



IV

action of catalysts (platinum or palladium) in the presence or absence of hydrogen. It possesses the same general properties as morphine.

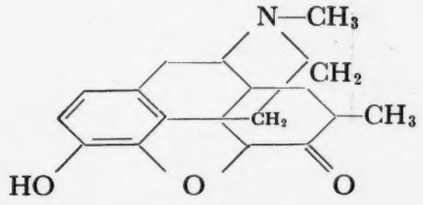
The methyl ether of dilaudid, dicodid® (dihydrocodeinone, V) may be prepared from



V

codeine in a manner similar to the synthesis of dilaudid. Acid hydrolysis of dihydrothebaine also gives dicodid. Isbell and Fraser[5] state that "the addiction liability of dihydrocodeinone appears to lie between that of morphine and codeine."

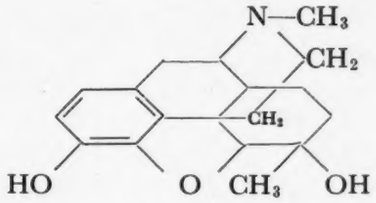
The constitution of metopon® (methyldihydromorphinone), which was synthesized by Small et al.[6] in a six-stage process starting from dihydrothebaine, has not been definitely established but is most probably represented by formula (VI). It has been studied clinically in



VI

cases of inoperable cancer[7–10] and the results indicate that it is a more potent analgesic than morphine with less pronounced addiction liability.

6-Methyldihydromorphine® (VII), synthesized by Small and Rapoport[11] by the action of

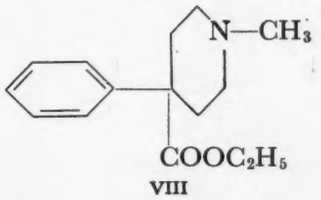


VII

methyllithium on dihydrocodeinone, is stated by Isbell and Fraser[5] to be as effective as morphine with much milder intensity of abstinence phenomena following withdrawal. Thus it appears that with metopon and 6-methyldihydromorphine some dissociation of physical dependence liability and analgesic potency has been achieved.

SYNTHETIC ANALGESICS

Meperidine and Related Compounds. Meperidine® (dolantin,® demerol,® pethidine,® etc., VIII), the first completely synthetic analgesic with

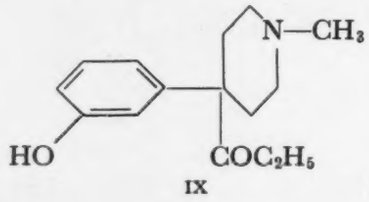


VIII

physiologic properties similar to morphine, was discovered by Eisleb and Schaumann[12] in 1939. While it does not bear a close chemical relationship to morphine, the two drugs do have several structural features in common such as a quaternary carbon atom, a phenyl group linked to this carbon, and an N-methylated heterocyclic nitrogen separated from the quaternary carbon by two methylene groups. Meperidine is about one-eighth[13] as effective as morphine; but even though signs of physical dependence may be milder than signs of dependence on morphine, the effects of chronic intoxication from meperidine are so pronounced that addiction to this drug is even more undesirable than is addiction to morphine.[5]

Replacement of the phenyl group of meperidine by *m*-hydroxyphenyl to give bemidone,® a slightly closer relative of morphine, does not appreciably alter the activity.[13] However, if this chemical change is accompanied by substitution of the ethyl keto (—COC_2H_5) for the carbe-

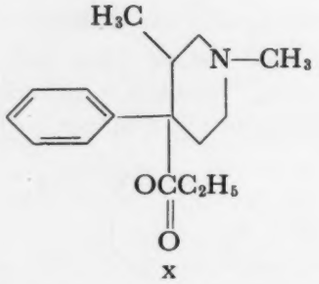
thoxy (—$CO_2C_2H_5$) group, a substance, ketobemidone (cliradon,® IX) is obtained which is



IX

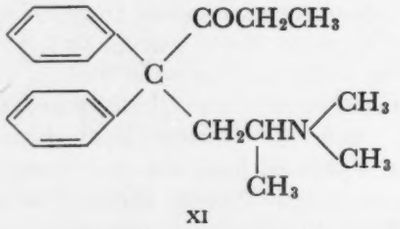
twenty times as effective[13] as meperidine but unfortunately has proved to be as addictive as heroin.

A final member of this series which should be included is *α-dl* 1,3-dimethyl-4-phenyl-4-propionoxypiperidine (nisentil,® X). It is reported by Houde et al.[9] to have a weaker analgesic action than morphine. It also shows properties of addiction.[14]



X

Methadone Series. The most striking development in the field of synthetic analgesics was the discovery of methadone,® *dl*-6-dimethylamino-4, 4-diphenyl-3-heptanone (XI).[15] Although it does

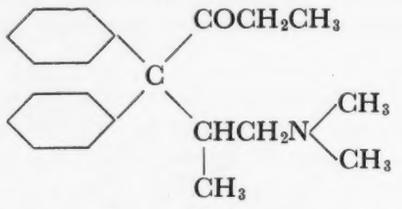


XI

have structural features common to both morphine and meperidine, there is one striking difference. Its tertiary nitrogen atom is aliphatic in nature in contrast to the heterocyclic nitrogen present in morphine and meperidine; it is well known that opening of the N-containing ring in morphine practically abolishes activity.[16]

Physiologically, methadone resembles morphine in most respects and is as potent an analgesic.[17] According to Isbell and Fraser,[5] "the total addiction liability of *dl*-methadone is probably almost as great as that of morphine." Isbell and Eisenman[18] further state that all of the analgesic effect and addiction liability reside in the *levo*-isomer.

dl-Isomethadone® (XII), which is produced along with methadone in the presently most

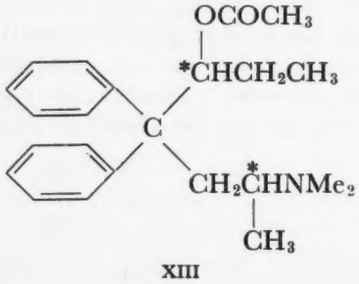


XII

practicable synthesis (starting from diphenylacetonitrile and chloroisopropyldimethylamine)[15] of the latter, is about one-half as active as methadone and appears to be equally addictive.[5] Again, only the *l*-isomer is effective.

Replacement of the dimethylamino group of methadone with morpholino, —N O, gives a drug which appears to be relatively ineffective and short-acting with quite low addiction liability.[5] It is marketed in England under the trade name heptazone.®

Reduction of the keto group of *dl*-methadone and its optically active forms yields two racemic and four optically active alcohols (*α*- and *β*-methadols),[19–22] by virtue of the formation of a new asymmetric center. These alcohols (except *α-l*-methadol) are very weak analgesics but the corresponding acetyl derivatives (acetylmethadols, XIII) are more effective than the methadones from which they are derived.[22] The *α-dl*, *α-d*, and *α-l*-acetylmethadols have been studied

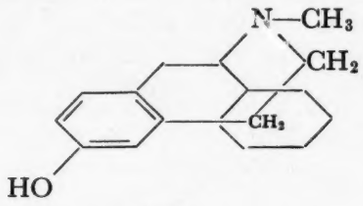


XIII

clinically by Fraser and Isbell[23] who report that all three possess addiction liability similar to methadone. It is particularly curious that *α-l*-acetylmethadol, which derives from the practically inert *d*-methadone, is a very potent drug with addiction liability equal to that of *l*-methadone. Both *α-l*-methadol and *β-d*-acetyl-

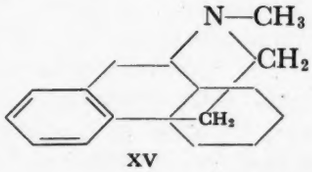
methadol which are also derived from *d*-methadone are almost as effective as morphine[22] and will substitute completely in addicted persons provided substitution is made twenty-four hours before morphine is discontinued.[24]

Morphinan Types. The synthetic analgesic most closely resembling morphine structurally is 3-hydroxy-N-methylmorphinan (dromoran,® XIV), which lacks only the oxygen bridge, the



XIV

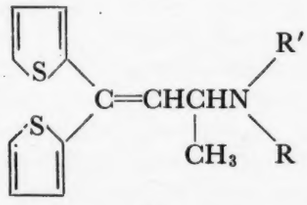
alcoholic hydroxyl and the isolated double bond of morphine. It was synthesized by the elegant method of Grewe et al.[25] Dromoran has four times the analgesic effect of morphine but is three to six times as toxic, with tolerance developing at the same rate as with morphine.[13,26] N-methylmorphinan® (XV), which lacks the



XV

hydroxyl group of dromoran, is also significantly active, though much less so than dromoran.

Dithienyl-butenes and -butanes. A final class of synthetic analgesics that deserves mention is the dithienylbutenes® (XVII). These substances bear

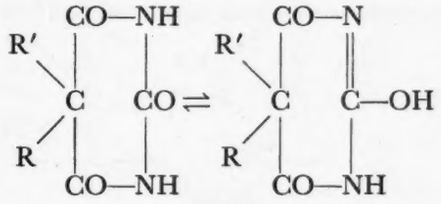


XVII

only slight chemical resemblance to the foregoing compounds although they do possess the branched methyl and tertiary amino group characteristic of methadone. Some of the dithienylbutenes are about as effective analgesic agents as morphine.[27,28] The most active member of the series ($R = C_2H_5$, $R' = CH_3$) is also as addictive as morphine.[28] Reduction of the double bond to give butane derivatives decreases activity.[23]

SEDATIVES (BARBITURATES) AND HYPNOTICS

Derivatives of barbituric acid in which the hydrogen atoms of the 5 position are replaced by alkyl, aryl or alicyclic radicals are commonly known as barbiturates (XVIII). They may exist in tautomeric form as indicated, of which the latter is capable of forming stable metal salts. Although barbituric acid has the atomic arrangement of nitrogen and carbon atoms that



XVIII

appears in pyrimidines it may also be looked upon as a ureide. Barbiturates are synthesized from urea and the appropriately substituted malonic acid ester.

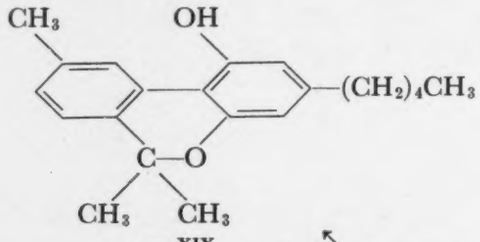
Addiction to these substances is common, is similar to chronic alcoholism and is "far more dangerous and harmful than is addiction to morphine or other analgesic drugs."[5] Barbiturates are used frequently by persons addicted to morphine, heroin, etc., between administrations of the narcotic to the extent that they develop a mixed addiction to the narcotics and to the barbiturates. The short-acting but potent nembutal® (pentobarbital, $R = C_2H_5$, $R' = C_3H_7\underset{\displaystyle CH_3}{\underset{|}{C}}H—$), amytal® [$R = C_2H_5$, $R' = (CH_3)_2CHCH_2CH_2—$] and seconal® ($R = CH_2{=}CHCH_2$, $R' = C_3H_7\underset{\displaystyle CH_3}{\underset{|}{C}}H—$) are preferred by addicts in the United States to the milder, longer-acting barbital® ($R = R' = C_2H_5$) and phenobarbital® ($R = C_2H_5$, $R' = C_6H_5$). The optimal relationship between activity and toxicity is produced when R or R′ is a branched aliphatic chain and when the sum of the carbon atoms in R and R′ is 7; e.g., amytal.[29] Withdrawal of barbiturates from individuals chronically intoxicated with these drugs is followed by a very severe and definite type of abstinence syndrome.[5]

Paraldehyde,® the trimer of acetaldehyde, chloral hydrate® [$CCl_3CH(OH)_2$], and alcohol

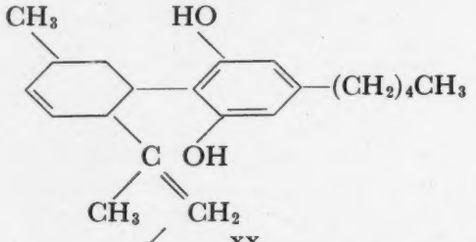
are three non-nitrogenous substances generally classified as hypnotics. Addiction to paraldehyde and chloral hydrate is relatively uncommon. The abstinence syndrome produced by these drugs is probably identical with that produced by the barbiturates.[30]

MISCELLANEOUS DRUGS

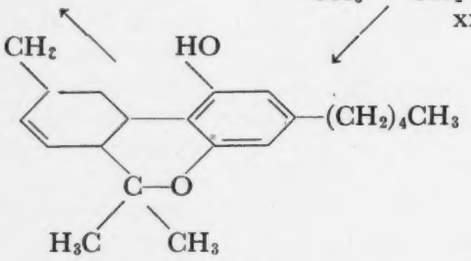
Marihuana. The chemistry of marihuana or hashish is still somewhat obscure. However, much light has been shed on this subject by the brilliant researches of Adams and co-workers who proved the structure of cannabinol® (XIX)[31]



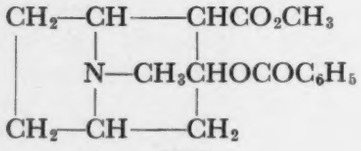
XIX



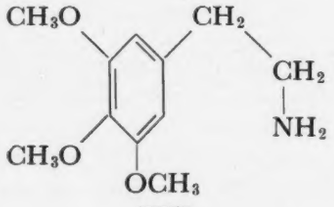
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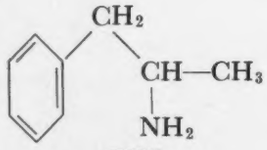
XXI



XXII



XXIII



XXIV

and cannabidiol® (XX)[32] (position of the isolated double bond uncertain), two components of the physiologically active "red oil" of Minnesota wild hemp, which were isolated by Adams, Pease and Clark.[33] Although cannabidiol is substantially devoid of marihuana activity and cannabinol only slightly active, Adams et al.[34] were able to isomerize cannabidiol to two isomeric tetrahydrocannabinols (XXI) (position of the double bond again uncertain) of high activity by a variety of mild reagents. A short while later Wollner et al.[35] isolated a tetrahydrocannabinol of high potency from "red oil" derived from charas of Indian origin, isomeric with but different from those prepared by the isomerization of cannabidiol. These authors conclude that "red oil" is probably composed essentially of cannabinol, cannabidiol and various isomeric (by virtue of the three asymmetric carbon atoms present and alternative locations for the alicyclic double bond) tetrahydrocannabinols, the properties of which may vary widely. It is noteworthy that no nitrogen is present in any of the "red oil" components.

Marihuana gives only mild intoxication except for scattered transient psychoses. No tolerance is developed and there is no abstinence syndrome.[30] Abuse of this drug has, nevertheless, become widespread and a social problem of considerable importance. Its abuse is frequently the first step on the road to morphine addiction.

Cocaine, Mescaline and Benzedrine. Cocaine (XXII), mescaline (XXIII), and amphetamine (benzedrine®) (XXIV) are a group of three stimulant drugs which are considered to be

addiction-producing. All three drugs contain nitrogen capable of quaternary salt formation. The amino group of cocaine, the alkaloid of coca, is tertiary, while both amphetamine and mescaline (the active principle of "mescal buttons" or "peyote") are phenethylamine types with a primary amino group. Knapp[36] has made an intensive study of amphetamine addiction and concludes that tolerance to this drug develops rapidly, so that addiction does occur, although it is infrequent and often relatively benign and that there are no withdrawal phenomena. Isbell[30] states that there is no tolerance developed to any of the stimulant drugs and that there are no true withdrawal symptoms.

SUMMARY

Analgesic substances that produce drug addiction with one exception, the dithienyl-butenes (XVII), have several structural features in common. These include a quaternary carbon atom, a phenyl group attached to this carbon, and an N-methylethanamine system likewise linked to the quaternary carbon. In addition all of the more potent drugs contain one or more oxygen atoms bound in various ways. About the only similarity of the aforementioned butenes to the other analgesic drugs is found in the tertiary amino group. Apparently some separation of addiction liability and analgesic potency has been achieved in metopon (VI) and methyldihydromorphine (VII).

The barbiturates (XVIII), although closely interrelated, bear little chemical resemblance to the analgesic drugs, in fact form salts with alkalies rather than acids. As is the case with the analgesic drugs, the barbiturates produce true withdrawal symptoms. Addiction to barbiturates may be more dangerous and harmful than is addiction to morphine. Alcohol, paraldehyde and chloral hydrate may produce addiction and result in abstinence phenomena similar to those of the barbiturates. On the other hand, mescaline, amphetamine, cocaine and the nonnitrogenous, active principles of marihuana produce no detectable withdrawal symptoms.

Therefore, only within a given chemical series with a specific similarity of biologic action, can one predict liability to addiction. Nevertheless, whatever their chemistry, drugs which produce effects pleasurable to certain individuals may result in addiction.

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The Phenomena of Tolerance*

M. H. Seevers, M.D. *and* L. A. Woods, M.D.
Ann Arbor, Michigan

Acquired tolerance is known to occur to a wide variety of chemical substances, of which morphine and its congeners are but classic examples. In the limited space available here the authors have chosen to focus attention on the broad aspects and possible mechanisms of tolerance development to morphine, utilizing data on related as well as chemically dissimilar compounds where reasoning by analogy appears to be indicated.

In sharp contrast to the situation which obtains concerning generally acceptable definitions of habituation and addiction, there is quite uniform agreement in the use and general understanding of the term "acquired tolerance" as it applies to morphine. In actual use, this term always represents a change from normal for a given individual or species. The reader should bear in mind, however, that during or subsequent to the tolerant state a condition may develop which is characterized by an absolute reduction in tolerance (acquired sensitivity) and which represents the unmasking of an abnormal cellular activity or response, or, as often expressed, a rebound sensitivity resulting from adaptive processes. Whether the underlying biochemical transformations which result in this prolonged state of increased irritability manifest themselves immediately after withdrawal in a greatly intensified form as the abstinence syndrome is not clear. In any case, the degree of sensitivity is subthreshold with respect to the usual overt signs of abstinence and requires special conditions to elicit its existence. It is conceivable that these changes may be manifest in man as behavioral changes.[1] For lack of better terminology we have designated this condition "post-tolerance sensitivity" to distinguish it from the abstinence syndrome although the former condition may be merely a prolonged but latent manifestation of the same biochemical alterations.

Although the phenomena of tolerance are considered here as separate entities for purposes of discussion, since they occur with many chemicals and exist entirely independently of any capacity of such agents to induce an addiction-like state, the conclusion is inescapable that in the clinical use of addicting narcotics the degree of physical dependence parallels, in a general way, the development of tolerance and does not occur in its absence.*

Several definitions of tolerance, essentially clinical in nature and related specifically to the opiates, have been quoted widely: " 'Tolerance' is a phenomenon characterized by the fact that more and more of a drug must be used to produce equivalent effects."[2]

"By tolerance is meant the gradual decrease in the effect produced by repeated administration of a drug; or, conversely, a gradual increase in the dosage of the drug necessary to produce the same effect as did the initial dose. It is probably true that tolerance ultimately becomes of such a magnitude that the effect of the initial dose cannot be reproduced by excessive doses."[3]

Since current interest focuses on the cell and the chemical molecule in the hope of elucidating

* Abraham Wikler and Harris Isbell have shown in man and animals that N-allylnormorphine early in the course of administration of morphine or methadone brings out evidence of developing physical dependence before there is any overt indication of development of tolerance. The authors do not believe this new evidence to be contradictory to the general statement above as it applies to ordinary clinical practice, in view of the wide quantitative differences both in time and in the severity of abstinence between N-allylnormorphine-induced and regular withdrawals. Furthermore, it must be borne in mind that N-allylnormorphine may possess pharmacologic actions other than those involved in "unmasking" of the abstinence syndrome.

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the basic mechanisms underlying the acquisition of tolerance, it seems that the time may be opportune to consider a definition which is couched in such terms. With this in mind, the authors propose the following: "Acquired tolerance is a phenomenon of cellular adaptation to an alien chemical environment characterized by a diminishing biological response."

Several terms to be used subsequently in this discussion require comment. For example the terms, tachyphylaxis and "acute tolerance" have been used by other investigators more or less synonymously. Whereas this usage may be satisfactory as it applies to compounds other than morphine (and possibly related compounds), Schmidt and Livingston[4] evidently conceived of something different than simple tachyphylaxis when they coined the term, "acute tolerance." The following represents our concept of, and usage of, these terms:

Tachyphylaxis—a rapidly developed and short-lived tolerance resulting from the oft repeated administration of a drug, usually by the intravenous route without necessary reference to, but not excluding, maximal receptor saturation.

"*Acute Tolerance*"—*saturation of tissue receptors* and hence *tolerance development* up to maximal within a *few hours* (either by oft repeated doses or by a large single dose). The degree of tolerance acquired is equal to that obtained following the "staircase" method of daily increment of dose covering weeks or months. In contrast to the situation that follows simple tachyphylaxis to other agents, other mechanisms are brought into play (possibly involving another type of receptor) which suggests the fundamental identity of "acute" and chronically developed tolerance to morphine and the like.[5]

Cross Tolerance—a diminished response of the tolerant cell or organism to other chemical agents of similar or dissimilar chemical structure or pharmacologic action.

Post-tolerance Sensitivity—a state of reduced tolerance (a state of sensitivity greater than normal for the individual) which occurs after complete disappearance of the tolerant state and persists for several months.

Intolerance—this term has been used by others to describe a sudden loss of tolerance during maximal drug administration, usually terminating fatally, with or without continued drug administration. Such a state has been described for man[6] and has been noted in the monkey,[7] dog[8] and rat.[9] Suggestions have been made that it may represent cardiovascular failure; a complete "metabolic breakdown" secondary to prolonged effects of morphine on the gastrointestinal tract resulting in diminished nutrition; or the breakdown of certain tissue barriers, e.g., the barrier which normally prevents accumulation of morphine in the spinal fluid.

Depression and stimulation are used here in the ordinary pharmacologic sense to describe the overt response resulting from the action of the drug without regard to the underlying cellular or physiologic mechanisms.

Receptor is used in its simplest possible connotation in view of our lack of knowledge concerning the nature of drug-cell interactions. The imagination of the reader might place this in any category from surface adsorption on the basis of physicochemical forces to firm chemical binding with cellular constituents.

Immunity as a synonym for tolerance has been avoided purposely in view of its specific use in regard to antigen-antibody relationships.

CHARACTERISTICS OF TOLERANCE TO MORPHINE AND RELATED COMPOUNDS

Certain characteristics of tolerance and its development to morphine and its congeners are sufficiently clear-cut to be almost pathognomonic of the phenomenon.

1. The first sign of tolerance in the ordinary clinical use of these drugs is a shortening of the duration of action following a given dose, or conversely, the necessity for increase in dosage to maintain a uniform duration of action. This situation engenders complaints from the patient that the drug is no longer effective in the condition for which it is prescribed. In the addict a change in behavior occurs and he reports dissatisfaction in obtaining the usual effects and requests a dosage increase.[1]

2. The above situation is soon followed, especially if the dose is rapidly increased or oft repeated, by the disappearance of the narcotic effects of the drug, which include mental depression, malaise, muscular weakness, loss of appetite, sleepiness and analgesia. From both an objective as well as from a subjective point of view this is a most striking manifestation of tolerance development. Tolerance is soon acquired to each new increment in dosage. This cycle, oft repeated, may result in a state of high-grade tolerance. In controlled experiments in man almost complete tolerance has been developed to 5 gm. per day of morphine.[10]

3. Qualitative and quantitative differences in the rate of development and completeness of tolerance occur,[11] and vary markedly with the (1) chemical compound, (2) animal species and (3) type of cell or group of cells involved. With morphine the situation in man is essentially as follows:[1]

Maximum tolerance development which in some instances is fairly complete: This state of affairs is rather uniform for man, monkey and the dog but not for the felines or rodents. In this category are included euphoria (sense of well being), narcosis (sedation), analgesia, hypnosis, respiratory depression, anorexia, vomiting, antidiuresis, hypothermia, peripheral vasodilatation (depressor action) and synchronization of the electroencephalogram.[1]

Inconsistent partial tolerance development: Bradycardia (vagal), miosis, gastric acidity.

Little or no tolerance development: Convulsant action, intestinal excitation, wheal development in man (histamine liberation?).

4. Tolerance development is slow and minimal to constant, small, and adequately spaced dosage; rapid and maximal with steadily increasing, oft repeated administration.

5. A grade of tolerance equal to that which may be obtained by "staircase" increments in dosage over weeks or months may be reached, in animals at least, in a few hours by saturating the tissues acutely with repeated large or even supralethal doses (death prevented by anticonvulsant drugs).[5] This type of situation is not possible in man because of the low native tolerance of the respiratory (and cardiovascular?) mechanisms to morphine. A maximal saturating dose in man is far beyond the lethal dose (respiratory failure), a situation which is unique to the primates.[2]

6. Cross tolerance exists in the following order of descending importance: (1) chemically similar phenanthrenes, (2) pharmacologically similar synthetic analgesics (some semblance of chemical similarity exists in these groups) and (3) pharmacologically similar, but chemically dissimilar substances (anesthetics, etc.).

7. Non-specific pharmacologic cross sensitivity exists to stimulants during withdrawal at a time when tolerance to morphine still exists in some tissues.[2]

8. The rate of disappearance of tolerance varies with the tissue affected and the ease with which tolerance is developed. Although there are exceptions to the rule, it may be said in general that there is an inverse relationship between the rate of tolerance development and its disappearance, e.g., (1) blood vessels gaining and losing acquired resistance in a matter of hours, (2) slowly developing tolerance such as to the emetic effect lasting for several months.[8] Tolerance disappearance is much more difficult to determine accurately than tolerance development since each test dose of morphine, administered to determine the rate of tolerance development, provokes into renewed activity those mechanisms responsible for tolerance development initially.

9. A state of reduced tolerance (post-tolerance sensitivity), as measured by an exaggerated response to the narcotic action, occurs after complete disappearance of all tolerance following prolonged and heavy drugging. This has been noted especially in monkeys by Kolb and Dumez[12] and by Irwin and Seevers,[13] being manifest as abnormal neurologic signs and in a reduction in absolute tolerance to the narcotic action. There is some evidence to indicate that post-tolerance sensitivity occurs in man although it may not manifest itself in exactly the same manner. This situation persists for many months after all of the original drug has been lost from the system, proof of the latter being based upon the failure of N-allyl-normorphine to precipitate the abstinence syndrome.[14] In man complete physiologic equilibrium may be delayed for a long time. This deviation is exhibited primarily in the psychic or neurologic areas, especially in what Wikler calls "conditioning" phenomena and in behavior patterns.

MECHANISMS INVOLVED IN TOLERANCE DEVELOPMENT

Factors Related to Access of the Drug to the Site of Action. One of the factors which has always been considered in relationship to the phenomenon of tolerance is that of prevention of access of the drug to the site of action either by (1) fixation at the site of administration or (2) reduction in permeability of one or more of the several membrane barriers through which the compound must pass in reaching the receptor site. Whereas it does seem to be reasonably well established that in certain instances some alteration occurs in the epithelial cells which modify the penetration of certain substances, e.g., in the cells of the intestinal tract for arsenic[15] and possibly in the cells of the oral cavity and upper respiratory tract for nicotine, there is little con-

vincing evidence to indicate that either of these mechanisms plays any significant role in the development of tolerance to morphine or related compounds.

Drug-cell Relationships. Receptor occupation: Schmidt and Livingston[4] reported a series of observations regarding tolerance development to the depressor and narc ic actions of morphine in the dog. This classic pharmacologic analysis proved beyond doubt that vascular smooth muscle and nerve cells (cerebrum, respiratory and vasomotor centers) became tolerant within a few hours following massive doses of morphine, to a degree comparable in every respect to that attained by prolonged administration of the drug over weeks and months of "staircase" increments in dosage. They state, "—it seems justifiable to assume that since the result of 'acute tolerance' is so similar to that of chronic tolerance the underlying cause is the same in both cases. This cause we believe to be a cellular change—of unknown nature—conditioned simply upon the presence of a concentration of morphine that equals or exceeds a critical level, initiated as soon as that level is reached, and maintained only so long as the concentration of morphine remains at or above that level."

Whereas these authors presented this analysis without any attempt to speculate concerning the nature of the "cell tolerance," they did emphasize the concept of critical levels of drug concentration, the latter being the essential feature of the present-day "receptor occupation" concept of tachyphylaxis to other chemical types. This hypothesis necessitates the assumption that drug molecules exert their pharmacologic action at the time of occupation of the receptor. Once attached they exert no effect other than to prevent the initiation of a new response by receptor combination with other molecules.

This concept of receptor occupation by molecules of the same type has received considerable emphasis as an explanation of tachyphylaxis, especially with reference to the sympathomimetic amines. The ease with which tachyphylaxis develops appears to vary with the number of molecules available; the smaller the dose required to elicit an effect, the less prominent the tachyphylactic phenomenon. As an example, no tachyphylaxis is developed to the pressor effects of epinephrine[16] in the dog, contrary to the situation with less potent agents.[17]

With respect to the sympathomimetic phenylethylamines, Winder et al.[17] studied six selected representatives as to the nature of tachyphylaxis developed to their nasal decongestant and pressor actions. By plotting cumulative nasal decongestant effects of amphetamine, desoxyephedrine and ephedrine on a probability scale against a logarithm of cumulative doses, they obtained a linear relationship. They pointed out that these results agree with the hypothesis that tachyphylaxis represents progressive receptor occupation, ultimately resulting in receptor saturation. These authors also emphasized the importance of metabolic disposal (detoxication or tissue redistribution) with respect to tachyphylaxis. Obviously, the more rapid the metabolic disposal, the slower will be the saturation of receptors. Attention was drawn to possible analogies between their work and those relating to the phenomenon of "acute" tolerance to morphine and even to chronic morphinism.

Many facets of morphine action and tolerance are amenable to explanation on the receptor occupation hypothesis, in fact, there are numerous actions of the drug which are difficult to explain on any other basis. For example, such well established facts as the following are in this category: (1) The logarithmic type of dose-response curve for analgesia and the rapid development of tolerance to this effect with large doses. (2) The phenomenon of cross tolerance and its relative specificity on a chemical basis, the effect being limited almost exclusively to compounds of a similar or closely related structure. (3) The effects of N-allylnormorphine as an antidote and "unmasking" agent. (4) The parallelism which exists between the depressor effect and the total tolerance development in the several animal species, e.g., non-rodent mammals (man, monkey, dog and cat) are sensitive to relatively small doses of the drug and uniformly develop a high grade tolerance to most of its depressant actions, including its depressor effects on peripheral vessels. On the other hand, rodents are relatively insensitive to most depressant actions of morphine (for example, no depressor effect occurs) and only a poor grade of tolerance is developed.

It is quite clear that although the best evidence and sound reasoning support the receptor occupation hypothesis as being invaluable as an aid in explaining many of the phenomena related to acquired tolerance, other equally important facts do not fit such a concept. It

seems necessary to invoke some other mechanism to account for a second type of tolerance of much lower grade and much greater persistence which is manifest especially during or following prolonged exposure to this class of compounds. A large body of evidence is accumulating to suggest that this tolerance may be based on a true and specific type of intracellular biochemical transformation. Some of the evidence which may be used to support the existence of the latter type of tolerance development is as follows: (1) Persistence of the abstinence syndrome long after the initial drug of addiction apparently has been removed from the body. (2) The nonspecific cross tolerance to chemically dissimilar substances such as alcohol, anesthetics, barbiturates, etc. This could hardly be explained on the basis of receptor saturation at least in the same sense as used above. (3) Enhanced sensitivity to convulsants during withdrawal. (4) The "post-tolerance sensitivity" which persists for many months after the cessation of withdrawal. (5) The vascular tolerance to thebaine and pseudomorphine, both agents conferring high-grade cross tolerance to morphine although neither agent exhibits any significant depressant action on the intact animal, nor is it capable of producing tolerance to the actions of morphine on the central nervous system. There are other examples but these will serve to support this point of view.

The completely differing responses of visceral and peripheral vascular smooth muscle to morphine, the former being solely excitatory, the latter depressant, has always offered a paradox which has been difficult to harmonize with the general concepts which are discussed here unless one postulates that two different types of receptors exist in these locations. Such a postulation seems unnecessary if we take recognition of the following facts: (1) Morphine is a liberator of histamine.[18] (2) The response of blood vessels in various locations and in the different animal species to exogenous histamine parallels almost exactly the response to morphine. This similarity was commented upon by Schmidt and Livingston[4] who suggested an action on the capillaries. (3) Neither acute nor chronic tolerance develops to histamine, and morphine-tolerant vessels retain full histamine sensitivity.[19] It might appear, therefore, that endogenous histamine is released at the time of receptor occupation by morphine, and that the differing pharmacologic actions on the two groups of vessels are secondary to this substance rather than resulting from a primary stimulant or depressant action of morphine itself. It is conceivable that a generalization such as this may apply to many types of smooth muscle. Along this line is the observation that a substance resulting from the mild oxidation of morphine is an exceedingly potent histamine liberator.[20,21] Whereas the antihistaminics will prevent the lethal action of this compound (which results from intestinal hemorrhage and shock) in intact dogs, they do not readily prevent its depressor action in anesthetized dogs.[22] This may be due in part to anesthesia but it is believed to result primarily from an inability of the antihistaminics to gain access to the site of endogenous histamine liberation or action. This concept is consistent with the known failure of the antihistaminics to antagonize completely many of the pharmacologic actions of histamine.

Time-dose relationships: Chen,[23] in his study of the optical isomers of ephedrine, reached the significant conclusion that the development of tachyphylaxis depended importantly upon the size of the dose, the interval between injections and the rate of injection. With regard to morphine the degree of tolerance development is directly proportional to the total quantity of the drug to which cells are exposed. In terms of receptor occupation this would imply maximal saturation of tissue receptors. This could be attained by a massive single dose which completely saturates for a variable period of time; or by oft repeated single doses which, if of adequate size, could maintain complete receptor saturation in the face of existing mechanisms of drug disposal. The corollary is that small nonsaturating doses at infrequent intervals will not evoke to the same degree the mechanisms necessary for tolerance development.

The above statements are based not only on experimental evidences but also on common clinical experience. It is a well known fact that many individuals can take fairly large and infrequent doses of morphine, or even small and regular doses of morphine if they be spaced adequately, without reaching a state in which the abstinence syndrome has any outstanding significance. These individuals also retain their sensitivity to the other actions of this compound.

Cross tolerance: The phenomenon of cross tolerance, which exists to a greater or lesser degree among homologous series of compounds capable of developing tachyphylaxis, is of fundamental importance and must be harmon-

ized with any concept regarding the basic nature of tolerance itself.

Among analgetic compounds the highest grade of cross tolerance occurs between morphine and its congeners (phenanthrenes). The cross tolerance which is developed to substances of similar pharmacologic actions (the methadone, meperidine and methorphinan series and other synthetic analgesics[24]) is somewhat similar but varies both qualitatively and quantitatively. This cross tolerance to compounds of quite similar chemical structure (phenanthrenes) or those possessing common functional groups (synthetic analgesics) could be harmonized with the concept of receptor occupation if we assume that each of these substances can make a partial or complete fit on the receptor by virtue of similar physicochemical properties.

In addition to the type of cross tolerance already mentioned, there is another type of cross tolerance which is of low grade and of a non-specific nature, and exists between morphine and compounds which are pharmacologically somewhat similar but are chemically dissimilar, e.g., the barbiturates, the volatile anesthetics and other drugs of a depressant type. That a certain degree of cross tolerance occurs under these circumstances is well known clinically, e.g., addicts are difficult to anesthetize and require larger doses of any depressant, especially during withdrawal.

This type of low-grade tolerance which is rendered permanent only after prolonged exposure to morphine would appear to invoke an entirely different mechanism than that involving simple and temporary receptor occupation. It would seem, in fact, to result from a semi-permanent change in the drug-sensitive cell as a result of some biochemical transformation which produces an increase in generalized irritability of the central nervous system. In this respect it differs from the short-lived and rapidly-developed tachyphylactic type of tolerance which is conferred by morphine to itself, and is crossed to other substances of a similar nature.

One of the essential requirements of the receptor occupation hypothesis as it applies to morphine is that only compounds with similar physicochemical properties could occupy the same receptors. Application of this hypothesis to the present situation would require, for example, that blood vessels, being rendered acutely tolerant to morphine in the dog and the cat, would still retain their complete sensitivity to dissimilar organic molecules such as the nitrites and histamine. Such is actually the case.

Cellular Adaptations Based upon Biochemical Transformation. The possibility that cellular adaptations (in the case of the neuron) based upon biochemical transformations may be one of the mechanisms of tolerance development, particularly when the administration of the drug is long continued, is of fundamental importance. Such transformation may occur at the biochemical (that is, enzymatic level) with or without detectable structural change. There is little doubt but that alterations of structure are, in the final analysis, reflections of extensive change in the biochemistry of cells. We have purposely shied away from the term, "biochemical lesion," for two reasons: every "lesion" is associated with biochemical changes, and the term, lesion, in its ordinary connotation implies something which can be detected by ordinary clinical procedures.

The concept of a biochemical transformation without morphologic change has precedence in bacteria in which enzymatic adaptation has long been regarded as a common phenomenon.[25] In the case of bacteria it is obvious that the rate of reproduction allows for the rapid appearance of mutants which have new biochemical characteristics. In this instance it is truly a biochemical mutation. The fact that yeasts undergo enzymatic adaptation in the presence of galactose in a period short of the time required for cleavage indicates that reproduction is not necessary for the phenomenon of enzymatic adaptation to occur.[26] Although in the mammalian organism many tissues (parenchymatous organs, epithelial tissues, etc.) may exhibit somatic mutation (requiring the formation of new cells), only enzymatic adaptation could develop in the neuron where complete regeneration is unknown. Because of the ordinary connotation of the term, mutation, we have preferred to use the term "biochemical transformation" in speaking of this condition.

There is no lack of evidence to support the existence of continual biochemical transformation in mammalian cells. Studies with isotopes have shown that practically all of the atoms present in the apparently stable structures (cell architecture determined by histologic means) of the cell are being exchanged fairly rapidly with other atoms of the same type.[27,28] This great variation in chemical structure occurs at

that level where most drugs could be expected to act. Therefore, since every molecule, whether it be enzyme, protein, nucleic acid, or what not, is in a state of constant change, the introduction of an alien chemical entity into the environment of such cells under various conditions could conceivably alter the enzymatic and protein mosaic by influencing synthesis. Cytochemical studies have demonstrated that the distribution and concentration of hydrogen ions, SH groups, nucleic acids, glycogen, alkaline phosphatase, acid phosphatase, lipoids, and the long-chain aldehydes in various areas in the hepatic cells of the liver are much affected by the physiologic condition of the animal, the diet, and by other factors extrinsic to the cell.[27] It has been demonstrated also that redistribution of enzymes in cells will alter function. For example, cyanide-sensitive respiration of cells of amphibian liver is eliminated by stratification of the cell contents by centrifugation, but returns when they have been restored to their normal positions.[27]

Biochemical transformations in the phenomenon of tolerance may conceivably take the form of (1) an increased or decreased (or complete destruction of) activity of those mechanisms normally operating to carry on a function or (2) initiation of new mechanisms, or bringing into primary position of importance existing alternative mechanisms or pathways to carry on the same function. In fact, both situations could exist simultaneously and be associated with alterations in the capacity of the cell to detoxify the chemical agent.

With respect to an increased capacity of the mechanisms operating normally, a few examples are cited here. Lightbody and Kleinman[29] have demonstrated that increased concentration of arginase in the liver of rats occurs as the result of feeding a high protein diet. This resulted without restoration in the quantity of the liver tissue in rats when the liver had been reduced in size by fasting. This is difficult to explain unless one assumes that the tissue responded to a given chemical stimulus by increased activity of a specific enzyme. Fishman[30] describes an increase in the β-glucuronidase activity of liver, kidney and spleen of dogs and mice which have been fed either borneol or menthol. Klein[31,32] has demonstrated an increase in liver d-amino acid oxidase in rats after thyroid feeding. There is an increase in ascorbic acid catalyzed oxidation of linolenic acid in the brain, as measured by the thiobarbiturate acid test, following repeated injections of morphine, meperidine, methadone and epinephrine in rats.[33] We have described an increased percentage conjugation of morphine in dogs newly tolerant to the drug.[34]

There are some examples to support the occurrence of partial or complete loss of activity of the original mechanism. For example, liver tissue from rats chronically intoxicated with a daily dose of 200 mg./kg. of morphine sulfate appears to have lost its ability to conjugate morphine.[9] Dogs[34] and rats[35] show a gradual diminution in the conjugation of morphine when maintained at a given level of dosage for a long period of time. Shideman and Seevers[36] reported that extra oxygen uptake resulting from the addition of pyruvate to incubated skeletal muscle mince in the case of morphine-tolerant rats is less than one-half of that which occurs with muscle taken from normal animals.

The possibility of the development of new enzymes or the uncovering of unused or alternative metabolic pathways in response to repeated chemical challenge should not be overlooked. A few examples will suffice to support the existence of such a possibility. The appearance of invertase in the plasma of dogs following the repeated injection of sucrose has been reported by Weinland.[37] Abderhalden[38] observed the appearance of proteolytic enzymes in blood following the injection of foreign proteins. The increased oxygen uptake of skeletal muscle from chronically morphinized rats during administration, with a further increase during withdrawal, suggests that there have been changes in certain phases of enzymatic activity.[39]

Very few investigations have been concerned with attempted correlations of biochemical with morphologic change. The most informative work of this type was carried out by MacNider,[40] who investigated the type of fixed cell response which develops in both the kidney and the liver of the dog as a reaction to injury induced by uranium nitrate. Severe injury to the epithelium of the kidney or liver resulted not only in epithelial regeneration and the appearance of atypical cells, but these mutant cells were relatively resistant to subsequent intoxication by uranium. In the case of the liver, cross tolerance also existed to the toxic actions of chloroform. Although the cells were altered morphologically they were functioning supposedly at a normal level. The latter conclusion was based on liver function tests with phenoltetrachlorphthalein. The present authors are not

entirely convinced of the validity of that conclusion in view of the (1) small number of tests with only one agent and (2) the wide variety of known functions of the liver. The possibility exists that there was a residual complement of normal cells of a sufficient number to give relative satisfactory values with the dye.

The paucity of evidence of this type would suggest that many individuals have concluded that studies aimed at elucidation of changes at the biochemical level are more likely to be fruitful than attempts to demonstrate alterations in cell morphology. Since changes in morphology should aid in defining the area of possible biochemical transformations, as will be discussed later, it seems that such studies involving a correlated attack should not be neglected.

Altered Metabolic Disposition of the Drug. 1. To a substance which is inert pharmacologically: Changes in the existing mechanisms of conjugation or degradation, or the development of new or alternative mechanism, may be involved in drug inactivation during the development of tolerance. The increased percentage of morphine conjugation, probably with glucuronic acid, in dogs[34] and rats[35] newly tolerant to morphine is an example of the former. During prolonged administration this increase disappears and is followed by a gradual decrease to a subnormal level in the quantity of conjugated morphine recovered. This reduction is paralleled by a diminution in the total quantity of recoverable free and conjugated morphine, suggesting the development of an alternative mechanism.

Whereas there are undoubtedly considerable changes in the capacity of the total organism to modify the morphine molecule in the sense indicated here, these changes standing alone cannot be considered to be a major factor in the development of tolerance. No investigator has been able to obtain values for changes which would even suggest that the body could more than double its capacity to alter all of the morphine administered. Since actual tolerance is measured in ten- and hundred-fold increases, detoxication does not offer a reasonable explanation of tolerance development.

It is conceivable that a new metabolic product formed at or near the site of cellular action might compete for receptors ordinarily utilized by morphine. For example, pseudomorphine formed *in situ* might have little or no narcotic effect *per se* but might result in blockade. To date there is no evidence for or against such a concept.

2. To a substance which is active pharmacologically: It was proposed first by Marme[41,42] that pseudomorphine (oxydimorphine) resulting from the oxidation of morphine in tissues might act as a stimulant substance which would antagonize the depressant action of morphine. This theory has never been accepted since no other investigator has been able to recover pseudomorphine from the tissues of morphine-tolerant animals. This is not surprising in view of difficulties which could certainly be anticipated from the known physicochemical characteristics of this compound and the very small quantity of morphine present in nerve tissue. The principal theoretical objections to this view have been: that pseudomorphine is unstable in alkaline solution, is precipitated by blood and is not antagonistic to morphine pharmacologically.[11]

The above arguments do not carry much weight in view of the fact that the solubility properties of pseudomorphine would almost insure its accumulation in tissues rather than blood should it be an *in vivo* product of morphine metabolism, since the acidity of tissues would probably keep it there. The fact that administration of exogeneous pseudomorphine does not antagonize the narcotic effects of morphine could be rationalized on the assumption that the compound does not gain access to the site of action from the blood stream because of failure to pass the blood-brain barrier. Some support for this concept is gained in the following fact: Pseudomorphine has a very low grade central action when administered even by vein. It does, however, possess marked depressor actions to which "acute" tolerance is rapidly developed, the latter being crossed completely to the depressor effects of morphine. Whereas blood vessels react to pseudomorphine just as does morphine, the cerebrum neither responds with tolerance nor does exposure confer cross tolerance to the narcotic actions of morphine.[43]

CORRELATIONS OF THE PHENOMENA OF TOLERANCE WITH A NEW CONCEPT OF MORPHINE ACTION

In 1929 Tatum, Seevers and Collins[2] presented a physiologic interpretation of morphine action based upon the best evidences available at that time. This concept has been termed the "dual action" theory because it visualizes a simultaneous existence of depression and stimu-

lation in different parts of the nervous system, tolerance being developed only to the former, the latter being manifest as the abstinence syndrome on withdrawal.

Actually this interpretation represents a concise and accurate description of events as they occur during administration and withdrawal rather than a theory designed to elucidate mechanisms. We find reason not to challenge but rather to confirm the broad tenets of this interpretation. It is our purpose to give substance to these tenets by formulating a hypothesis in more specific terms in light of the new evidence which has been obtained in the last twenty-five years, much of it in our own laboratories, and as yet unpublished. The principal deviation from the original interpretation is a concept of the dual action of morphine as a manifestation of simultaneous depression and stimulation of the same cell, the neuron.

During the last decade new chemical tools have come into our hands, the synthetic analgesics and N-allylnormorphine. Furthermore, our concepts of drug-cell relationships have broadened greatly as they relate to "receptors" and biochemical adaptations. An acceptable hypothesis which would explain the simultaneous existence of depression and excitation in the same cell, the diverse effects on various types of cells during acute and chronic poisoning and the phenomena of tolerance and physical dependence in the several animal species involves more assumptions than proof and leans heavily on reasoning by analogy in view of our meager knowledge of cell-drug relationships. We have attempted to present what appears to be as simple a concept as might rationalize the known facts.

Limitations of space will restrict this discussion to the most pertinent facts upon which these views are based. The crucial variation from the "dual action" interpretation, as originally outlined, is that depression and stimulation are conceived of as existing simultaneously in the same cell (the neuron) rather than in different cell groups. This concept has been made possible by the observations of Irwin and Seevers[13] that single large sub-lethal doses of several representatives of the meperidine, methadone and methorphinan series of drugs induce, in a matter of hours, a neurologic syndrome in the Rhesus monkey which is characterized by an increase in the deep reflexes, hypertonicity of the flexors and abductors of the lower limbs, hypertonicity of the extensors in the upper limbs and occasionally of the flexors. In addition, there may be observed disturbances in gait, overreaching in the forelimbs, increased or decreased motor activity, asymmetric pupils, apprehension, convulsions, or the animal may be completely paralyzed and strikingly resemble a decorticate preparation. This state may remain temporarily and disappear almost completely or, if it is present in severe form and precautions such as tube-feeding are taken to insure survival, will result in a permanent effect. Neuropathologic examination by Professor Scharenberg of the Department of Neuropathology[44] indicates that the lesions are limited to diffuse demyelination of the corona radiata of the cortex, with sparing of the arcuate fibers. A similar type of lesion has been observed in the monkey following chronic administration of methadone in these laboratories[13] and probably can occur with morphine and heroin in view of the description of similar neurologic signs by Kolb and DuMez.[12] These have not been noted with the latter compounds in our laboratories. Prior administration of N-allylnormorphine, the specific antagonist, will prevent completely the neurologic signs as well as the subsequently developed lesions.

This evidence appears to prove rather conclusively that (1) these compounds occupy receptors on certain myelinated neurons, (2) they exert a pharmacologic or pathologic effect after occupation and (3) N-allylnormorphine competes successfully for the receptors ordinarily occupied by these agents, or displaces the agent after occupation. These observations have naturally attracted our attention to the axon as a probable point of action of these drugs. Essential features of our present concept are as follows:

Morphine and its congeners and the synthetic analgesics combine with receptors located at two different sites on the same neuron: (1) on or near the surface of certain medullated axons of internuncial neurons; (2) in the cell body of the same or other neurons. Receptor-drug combination at the two different cell sites, although possibly involving the same molecular configuration or "anchoring" groups, results in an entirely different sort of response in the cell as follows:

Receptor-drug combination on the axon is visualized to be essentially a surface phenomenon depend-

ent upon physicochemical forces, the pharmacologic response occurring only at the time of receptor occupation by the drug. The axon-drug interaction is characterized by rapidity of combination, the ease with which the bond is broken, and rapidity of return of function when the drug is displaced. The degree of blockade is proportional to the number of receptors in any given neuron and is a logarithmic function of the degree of receptor occupation. Partial receptor occupation results in tachyphylaxis, maximal but not complete saturation in "acute" or chronic tolerance.

Receptor-drug combination in the cell body is visualized to require intracellular penetration, to be slow in onset, firm in combination and long-lasting, the action being proportional (within limits) to the quantity present. The pharmacologic response to this drug-receptor interaction is cellular excitation which lasts throughout the whole period of receptor occupation with the drug (or its degradation product), in this sense differing from the action of the drug on the axon. This excitation may be viewed either as a direct effect of the drug to accelerate metabolic processes (coenzyme-like, thyroid-like) or as a metabolic inhibitor (cyanide-like). Prolonged occupation of the receptor at this intracellular site (contrary to the effect on the axon which results in a nullification of the response) brings into being a series of cellular reactions, of an unknown nature, creating a state of excitability in the cell body which, on the basis of present knowledge concerning the fate of morphine, outlasts the presence of morphine in the cell. In fact, evidence suggests that the ultimate in this process is the creation of a semipermanent (or even permanent) alteration of the biochemical composition of these cells.

In applying these basic concepts to the known facts as they occur in the intact animal we conceive of *narcosis, analgesia and motor weakness* as resulting from partial blockade of axon conduction in internuncials in the brain and cord; *tolerance* (1) to the high-grade and specific type of tachyphylactic response as a maximal, but never complete, saturation of axon receptors; (2) the low-grade, non-specific type of tolerance to result from the increased excitability of the cell body; *cross tolerance* (1) to agents with similar "anchoring" groups as a competitive, partial receptor saturation on the axon; (2) to non-specific depressants (alcohol, barbiturates, and the like) to result from increases in the general excitability in the cell body; *the abstinence syndrome* as an unmasking of the state of increased excitability in the cell body of the neuron, its appearance coinciding with the loss of morphine from its receptor site on the axon thus permitting increases in axonal conduction.

We visualize the antagonistic action of N-allylnormorphine to result from satisfactory competition of this agent for morphine (or other agents) for the receptor site on the axon and possibly to some extent at the intracellular site, in view of its capacity to prevent convulsions and other manifestations of stimulation. A similar explanation would fit its capacity to unmask the abstinence syndrome. Other actions of N-allylnormorphine are more easily explained on the assumption that this compound is not without its own pharmacologic action, possibly as a synergist with morphine, especially at the intracellular site.

Wikler's classical studies in the spinal dog[1] and man[45] in which he can duplicate the phenomenon which occurs during administration and withdrawal of morphine furnishes us with a simple preparation upon which to test this hypothesis, especially since he has localized the principal site of depression at the internuncial neuron. Events which occur in the activity of certain reflexes such as the flexor and crossed extensor reflexes (both involving internuncial neurons), and the knee jerk (two-neuron arcs) can be harmonized readily with this hypothesis. His observation[45] that physostigmine produces changes in the hind limb reflexes of tolerant spinal dogs which resemble those seen during abstinence from morphine or methadone appears to be easily reconciled with the position that excess acetylcholine at the synapse would unmask the state of increased excitability in the cell body, the degree of resulting discharge being adequate to overcome any existing axon blockade (which at best is never complete). In this regard, it should be well to call attention to the differences, as we visualize them, between the incomplete axon blockade with the analgesics and the blockade produced by the local anesthetics, the latter involving firmer binding, possibly on a solubility basis, with the axon and representing a more complete blockade. This view is in harmony with the physicochemical characteristics of these substances as they relate to lipid solubility. New evidence supports this

view in indicating that the molecular concentration of morphine in brain and fat is exceedingly low.[46]

In order to harmonize this hypothesis with known facts it becomes necessary to postulate a wide species variation with respect to number and location of receptors. For example, it would be necessary to conceive that felines and hoofed animals lack receptors on axons of internuncials which carry motor impulses.

Due to limitations of space we have made no attempt to discuss the phenomena of tolerance as they relate to other addicting drugs, such as alcohol and the barbiturates. It is quite clear that with these agents tachyphylaxis as defined here does not occur, consequently the tolerance which is developed is of a relatively low grade. We believe, therefore, that the increased excitability of the neuron following prolonged exposure to these agents more closely approximates that which we have described for the cell body although obviously involving different types of receptors and possibly different basic mechanisms.

We have presented here only the bare outline of the hypothesis and without adequate supporting data, the latter being published elsewhere. The actions of morphine on tissues other than the neuron are explained most easily if it is postulated that receptors on smooth muscle are of the surface type involving essentially physicochemical forces, in view of the ease with which tachyphylaxis is developed; whereas those in the cells of skeletal muscle are somewhat analogous to those in the cell body of the neuron and invoke biochemical changes. The latter view is in harmony with the observations of Shideman and Seevers[36] on the azide-sensitive increment in cellular oxidations observed in skeletal muscle obtained during withdrawal from morphine tolerant rats and other animals.

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Clinical Characteristics of Addictions*

HARRIS ISBELL, M.D. *and* WALTER M. WHITE, M.D.

Lexington, Kentucky

THE purpose of this paper is to outline the clinical symptomatology of acute and chronic intoxication with the addicting drugs (with the exception of alcohol) that are of importance in the United States, to compare the development of tolerance to certain of these substances, and to discuss and contrast the clinical manifestations which follow abrupt withdrawal of some of these drugs.

The Expert Committee on Drugs Liable to Produce Addiction of the World Health Organization has adopted the following definition of addiction: "Drug addiction is a state of periodic or chronic intoxication detrimental to the individual and to society, produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include: (1) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means; (2) a tendency to increase the dose; (3) a psychic (psychological) and sometimes a physical dependence on the effects of the drug."[1] Two of the features of this definition require some comment. Addiction always implies consumption of drugs in amounts that produce effects detrimental either to the individual or to society. In other words, addiction is always a matter of abuse, not of proper use. It is also important to note that physical dependence (a withdrawal illness) is not a necessary feature of all addictions.

Under the terms of this definition the addicting drugs of importance in the United States are: (1) opiates and synthetic analgesics (opium, laudanum, paregoric, morphine and morphine derivatives, methadone® and meperidine®); (2) hypnotic and sedative drugs (barbiturates, chloral hydrate, paraldehyde and bromides); (3) alcohol (because of lack of space, addiction to alcohol will not be discussed in this paper); (4) cocaine; (5) certain sympathomimetic amines (amphetamine and methamphetamine); (6) mescaline (peyote®) and (7) marihuana.

ADDICTION TO OPIATES AND SYNTHETIC ANALGESICS

Characteristics of Opiate Addiction. Addiction to opiates is usually described as having three important characteristics: (1) tolerance, (2) physical dependence and (3) emotional dependence.[2] By *tolerance* is meant a decreasing effect on repetition of the same dose of a drug. This particular characteristic is very marked in addiction to the opiates and synthetic analgesics. Patients with well developed tolerance have injected as much as 5 gm. (78 gr.) of morphine sulfate intravenously in less than twenty-four hours without developing significant toxic symptoms. Tolerance to the various effects of morphine and related drugs develops, however, at different rates and in different degrees. For example, tolerance to the toxic, sedative, emetic, analgesic and respiratory-depressant effects of morphine develops very rapidly and becomes marked, whereas tolerance to the miotic effects and to the spasmogenic effects on gastrointestinal smooth muscle, if developed at all, is never complete.

Physical dependence refers to the development of an altered physiologic state which requires continued administration of a drug to prevent the appearance of a characteristic illness, termed an "abstinence syndrome." Physical dependence is an extremely important characteristic of addiction to morphine and similar drugs, since it leads to continuity of intoxication with resultant subservience of all phases of the addict's life to the one aim of obtaining and maintaining a constant supply of the drug.

Emotional dependence is defined as a substitution of the use of the drug for other types of adaptive behavior. In other words, use of the drug becomes the answer to all of life's problems. Instead of taking constructive action about his difficulties, regardless of their type, the addict seeks refuge in his drug.

* From the National Institute of Mental Health, Addiction Research Center and the Clinical Division, Public Health Service Hospital, Lexington, Ky.

ADDICTION TO MORPHINE

Addiction to morphine may be used as a prototype of addiction to analgesic drugs. Ordinarily, individuals with a psychologic make-up which renders them susceptible to addiction are introduced to drugs as a result of association with persons who are already addicted. Proper therapeutic administration of morphine seldom leads to addiction, except when administration is justifiably prolonged, adequate pain relief becoming more important than probable addiction. Most frequently, but not always, new addicts are recruited among members of minority groups growing up in economically depressed areas of the larger cities. In our particular culture males are more susceptible to addiction than are females. Most often addiction begins in the third decade of life but the onset may be between the ages of fifteen and twenty years. Boys who are drifting into or living near the delinquent fringes of society are particularly susceptible. Ordinarily, the adolescent addict has some knowledge about drugs and about addiction before he begins their use. Experimentation with marihuana may precede experimentation with morphine or heroin. In the beginning of addiction the drug is usually taken either as a snuff (heroin) or subcutaneously (morphine). Regardless of the initial route of administration, the addict usually changes to intravenous administration of the drug as addiction proceeds. Initially, the potential addict takes the drug only occasionally ("joy popping"); later he begins to use it daily and, finally, as tolerance develops, he begins to increase the dose and to shorten the interval between injections. The need to obtain more and more of the drug almost inevitably leads to delinquency, to antisocial behavior and to illegal acts.

The symptoms of intoxication with morphine prior to the establishment of tolerance vary with the individual, the amount of the drug taken and the route of administration. In the majority of persons the first doses of morphine taken without medical need produce unpleasant symptoms such as nausea, vomiting, pallor, sweating and itching. These may deter the potential addict for a time but as he continues to experiment with the drug he comes to value these unpleasant effects, since they indicate that the drug is strong and effective. Prior to the development of tolerance the drug induces slowing of the respiratory and pulse rates, decreases body temperature and reduces blood pressure slightly. The conjunctivae are usually reddened, the eyelids droop slightly and blinking of the eyelids is less frequent. There is no nystagmus, slurring of speech or ataxia. Appetite is lessened, sexual drive is diminished and the sensation of fatigue is abolished. In the nontolerant individual morphine may induce a short period of increased psychomotor activity manifested by increased loquaciousness and a burst of ill directed physical activity, such as mopping, sweeping, etc. If the dose is sufficiently large, increased activity is succeeded by a period of drowsiness and hypoactivity. The addict may drift into a light sleep, suddenly awaken, and then drift back to sleep. This state is termed "being on the nod" or, by the younger generation of addicts, "goofing off." It is in this peculiar state of alternating somnolence and wakefulness that opium dreams occur. The dreams are not exceptionally beautiful but are identical with fantasies in which the patient indulges when not taking morphine. The use of the drug simply facilitates indulgence in fantasy.

Intravenous use of morphine or similar substances produces dramatic physiologic and psychologic effects. Within a few seconds after an intravenous injection of morphine the addict experiences sudden dizziness; the blood vessels of the skin and mucous membranes dilate, the resultant flushing being most prominent over the upper half of the body; intense itching occurs; and a rumbling sensation is felt in the stomach. When questioned carefully most addicts will compare the effects of the intravenous administration of morphine to a sexual orgasm,[3] except that the sensation is referred to the abdomen rather than to the genitals. When heroin, dilaudid or methadone are used the transient dizziness is greater, and flushing, itching and tinkling are absent. Many addicts prefer these latter drugs because of the absence of the "needles and pins" sensation. The acute effects of an intravenous injection subside within a few minutes. The symptoms thereafter are identical with those observed following subcutaneous administration.

Symptoms during Maintained Addiction. As the addict becomes tolerant the state of semisomnolence disappears, respiratory and pulse rates become normal, blood pressure is normal and temperature is usually at the upper limit of the normal range. The pupils, however, remain

constricted and constipation is always present. If a sufficient supply of the drug is available, the overt behavior of the addict is not unusual and he can carry on a highly skilled, technical occupation in a fairly satisfactory manner. Emaciation, which is frequently observed, is a secondary effect and is due to the addict using most of his money for drugs rather than for food. The only signs of addiction present may be needle marks, tattooed scars over the veins and constricted pupils. If drugs are difficult to obtain and the addict cannot maintain a constant supply he will experience symptoms of abstinence, will be nervous and may be absent from work or school. Marked changes in sexual activity occur during addiction to opiates. Libido declines in both males and females so that the frequency of intercourse is greatly diminished. While the male does not become impotent, the length of intercourse necessary to obtain an orgasm is greatly increased. Women usually cease to menstruate and pregnancy is rare.

The Morphine Abstinence Syndrome. If morphine is withheld from a person who is strongly addicted to that drug, a self-limited illness appears which constitutes one of the most stereotyped syndromes in clinical medicine. During the first twelve to fourteen hours of abstinence there are no obvious symptoms or signs; then occasional yawning, light perspiration, rhinorrhea and mild lacrimation are likely to appear. The addict usually goes into an abnormal tossing, restless sleep (the "yen"). After eighteen to twenty-four hours of abstinence the patient awakens and, thereafter, has insomnia. Yawning, rhinorrhea, lacrimation and perspiration becomes much more marked; dilatation of the pupils and recurring waves of gooseflesh are seen. Twitching of various muscle groups occurs. The patient complains bitterly of severe aches in the back and legs and of hot and cold "flashes." The addict usually curls up in bed, his knees drawn up to his abdomen and covers himself with as many blankets as he can find, even though the weather may be hot. He continuously twitches his feet. After about thirty-six hours restlessness becomes extreme; the addict moves from side to side in the bed, gets in and out of bed and is constantly in motion. Frequently this hyperactivity leads to chafing of the skin on the elbows and knees. The patient begins to retch, vomit and have diarrhea. Concomitantly, the intensity of all the other signs increases and the addict is unable to sleep. He eats and drinks very little and loses weight rapidly, sometimes as much as 10 pounds in twenty-four hours. He becomes disheveled, unkempt, unshaven, dirty and extremely miserable. Respiration usually increases, particularly in depth, blood pressure rises 15 to 30 mm. of Hg and body temperature is elevated about 1°C. Symptoms reach peak intensity forty-eight hours after the last dose of morphine is administered, remain intense until the seventy-second hour of abstinence and then begin to decline. After seven to ten days all objective signs of abstinence have disappeared, although the patient may still complain of insomnia, weakness, nervousness and muscle aches and pains for several weeks.

Like any other biologic phenomenon, the morphine abstinence syndrome varies somewhat, both qualitatively and quantitatively, in different individuals. Thus in a group of persons addicted to 240 mg. of morphine daily, a few will show only mild abstinence symptoms following withdrawal; most will have moderately severe symptoms; and a few will be quite ill. Some patients vomit repeatedly; others never vomit.

A sufficiently large dose of morphine, or some equivalent drug, abolishes symptoms of abstinance within a very few minutes. It is a dramatic experience to observe a miserably ill person receive an intravenous injection of morphine, and to see him thirty minutes later shaved, clean, laughing and joking. The emotional significance of this abrupt reversal of the withdrawal illness is discussed in the paper on "The Psychiatric Aspects of Drug Addiction."

Within limits, the intensity of the abstinence syndrome is dependent upon the dose the individual has been receiving.[4] The relationship of the dose to the intensity of the syndrome is, however, an exponential function, so that increasing the dose of morphine beyond 480 to 600 mg. of morphine sulfate daily does not cause a significant increase in the severity of the abstinence syndrome.

Addiction to Other Opiates. Addiction to all preparations containing opium, and to all the commonly used drugs that are chemically related to morphine, qualitatively resembles addiction to morphine. A high degree of tolerance can be developed to any of these substances and such differences as do exist in the rate of development of tolerance are not of

great practical significance. The chief differences in addiction to these various drugs are related to differences in potency and length of action. Heroin, metopon and dilaudid are more potent than morphine so that, in terms of weight, the amounts taken are smaller. The length of action of these three compounds is shorter than that of morphine so that the number of doses required per day is greater. Due to the short length of action, signs of abstinence from these three drugs appear earlier, reach peak intensity sooner and decline more rapidly than signs of abstinence from morphine. The length of action of dromoran® is somewhat longer than that of morphine so that withdrawal symptoms appear more slowly, are somewhat less intense and subside more slowly than the abstinence syndrome of morphine. Codeine, being far less potent than morphine, is less frequently a drug of addiction but when addiction to codeine does occur the amounts consumed may be enormous (2,400 to 3,600 mg. daily). Signs of abstinence from codeine appear more slowly, are less intense and somewhat more prolonged than signs of abstinence from morphine. Dihydrocodeinone (hycodan®) is far more potent than codeine and so is greatly preferred by addicts to codeine. The intensity and time course of the dihydrocodeinone abstinence syndrome lie between that of morphine and codeine. Since the effects of opium and of preparations containing opium are due to the morphine content of the opium, addiction to these substances does not differ significantly from addiction to morphine.

Addiction to Methadone. Methadone is a synthetic analgesic drug which chemically is not related to morphine. The pharmacologic effects of methadone, however, closely resemble those of morphine in both animals and in man. Length of action of methadone in man is considerably longer than that of morphine so that cumulative effects appear in non-tolerant individuals when several small doses are taken daily. Tolerance to methadone is less complete and develops somewhat more slowly than does tolerance to morphine. The drug may be taken orally, subcutaneously or intravenously. It is quite irritating and, if injected intravenously at frequent intervals, causes extensive phlebothrombosis. Injection of large amounts subcutaneously causes marked induration of the skin and subcutaneous tissues. Physical dependence on methadone definitely does occur.[5] Signs of abstinence appear slowly (are usually not evident until the third or fourth day of withdrawal) and are less intense than signs of abstinence from morphine. Subjective symptoms of abstinence (weakness, fatigue, aching and insomnia) may be present for six weeks following withdrawal.

Addiction to Meperidine (Demerol®). Addiction to meperidine requires special comment for two reasons: the belief that this drug is not addicting is still widespread and the incidence of addiction to meperidine among physicians and nurses is so high that one could justifiably speak of it as "the doctors' and nurses' addiction." The increase in addiction to meperidine is reflected in the admission figures of the Public Health Service Hospital at Lexington, Kentucky. Between July 1, 1946, and July 1, 1947, only six meperidine addicts were admitted to this institution. Between July 1, 1950, and July 1, 1951, 268 meperidine addicts entered this hospital. All of these 268 persons were regarded as "primary" meperidine addicts (persons who had not been, so far as could be ascertained from their histories, addicted to any other drug). Forty-four of the 268 meperidine addicts were physicians, 44 were nurses, and 9 were medical technicians or nurses aides.

Subjective effects induced by meperidine differ somewhat from those of morphine. The drug causes considerably more dizziness and a greater degree of elation. The length of action of meperidine is relatively short so that addicted persons ordinarily take the drug subcutaneously or intramuscularly at intervals of only two to three hours, both day and night. Since the drug is fairly irritating, marked induration of the skin and muscles occurs and large skin ulcers may be present. Human addicts develop a significant degree of tolerance and may elevate their doses to levels of 1,000 to 4,000 mg. daily. Tolerance to the toxic effects, however, is not complete, so meperidine addicts may show twitching of the muscles, tremors, mental confusion, hallucinations, dilated pupils, dry mouth and, at times, convulsions.[7] The electroencephalogram may be quite abnormal, showing paroxysmal bursts of slow voltage high waves and spike and dome discharges.[6] Impairment of ability to work is far greater than in the case of addiction to morphine.

Abstinence from meperidine resembles abstinence from morphine.[7] Due to the short length of action, signs of abstinence are evident in three to four hours and reach maximum intensity

eight to twelve hours after the last dose. Thereafter, signs of abstinence decline rapidly and usually disappear completely in four or five days. At peak intensity, restlessness and nervousness are far worse than during abstinence from morphine. Twitching of muscle groups, which may become so gross as to involve entire extremities, is frequently observed. The usual autonomic signs (yawning, mydriasis, etc.) are present but are less prominent than during abstinence from morphine.

ADDICTION TO HYPNOTICS

Barbiturate Addiction. Barbiturate addiction can be used as the prototype of addiction to hypnotics. It is wise to reiterate that barbiturate addiction implies habitual consumption of amounts of barbiturates far in excess of those used therapeutically. There is no evidence that significant physical and emotional dependence occur in patients who consume only the usual therapeutic doses of these drugs. Addiction ordinarily does not occur unless the patient is consuming 0.8 gm. or more of one of the potent, quickly-acting barbiturates daily.

In general, the etiology of barbiturate addiction resembles that of addiction to morphine. Personality abnormalities are of prime importance, with various types of neuroses and character disorders being the most prominent diagnostic categories in this type of addiction. Addiction to alcohol or opiates is frequently involved in the genesis of barbiturate addiction. Addiction to barbiturates is frequently a mixed intoxication, with concomitant abuse of both alcohol and amphetamine being very common.

Barbiturate addicts usually take the drug orally. Occasionally, opiate addicts may attempt to inject the contents of the capsules. Since the barbiturates are quite irritating this practice frequently leads to formation of large skin ulcers. Any of the common types of barbiturates may be used but addicts prefer the potent, quickly-acting drugs, such as pentobarbital (nembutal®), secobarbital (seconal®) and amobarbital (amytal®) to the less potent, slowly-acting preparations, such as phenobarbital and barbital. Ordinarily barbiturate addicts consume the drugs at intervals throughout the day, with the greatest quantities being ingested at night.

Intoxication with barbiturates resembles intoxication with alcohol. The symptoms include impairment of mental functioning, loss of emotional control, poor judgment, confusion, abnormal behavior of various types and, occasionally, a toxic psychosis. Objectively, nystagmus, dysarthria, ataxia in gait and station, and adiadokokinesis are prominent signs. The electroencephalogram shows a characteristic fast pattern. Coma is unusual. Respiratory rate and minute volume are not greatly depressed. Inanition is not a prominent feature of uncomplicated barbiturate addiction and, if present, suggests that the addict is also using large amounts of amphetamine or alcohol. The intensity of symptoms of intoxication varies from individual to individual and in the same individual from day to day. These variations are partly related to food intake, since the effects of the barbiturates appear sooner and are much more intense if the drug is taken into an empty stomach.

Although partial tolerance to barbiturates does develop it is never complete. Each individual has a definite limit to his tolerance and if the dose is elevated, even 0.1 gm. daily above this level, the degree of intoxication markedly increases. For this reason acute poisoning may occur in a chronically intoxicated individual.

Definite abstinence symptoms follow withdrawal of barbiturates.[8] Intensity of symptoms of abstinence varies with the dose the addict has been consuming, the length of time he has been addicted, the degree of intoxication produced by the doses he was consuming, and with individual factors which are not understood. Following abrupt withdrawal of barbiturates from persons who have been consuming 0.8 gm. or more of barbiturates daily, symptoms of intoxication decline during the first eight hours and the patient appears to improve. As the signs of intoxication decline, increasing anxiety, nervousness, headache, twitching of various muscle groups, tremor, weakness, impaired cardiovascular responses on standing and vomiting become evident. These symptoms usually become fairly intense after sixteen hours and are quite severe after twenty-four hours of abstinence. As the symptoms develop the electroencephalographic pattern shows progressive slowing. Eventually, paroxysmal bursts of high-voltage slow waves and spike and dome complexes are noted. Between the thirtieth and forty-eighth hours of withdrawal, convulsions of *grand mal* type are very likely to occur. Occasionally, seizures are observed as early as the sixteenth hour of abstinence and as late as the

eighth day. The convulsions may be preceded or followed by bouts of uncontrollable twitching of the face and in one or more extremities. In all probability these represent abortive or "minor" seizures. Following convulsions the patients usually are confused for a time. After an hour or two confusion lessens and some patients may recover without further incident. Others develop increasing insomnia culminating in a delirium, which is likely to begin and to be worse at night. The delirium is characterized by confusion, marked tremors, disorientation in time and place (usually not in person), hallucinations and delusions. Hallucinations are predominantly visual although auditory hallucinations do occur. The types of hallucinations which occur are extremely variable and resemble those seen in delirium tremens. The patient's reaction to the delirium varies from one of amusement at the queer people and animals he is observing to one of extreme agitation, anxiety and frantic attempts to escape from imaginary persecutors. Agitation may lead to extreme exhaustion and even to death.[9]

Like abstinence from morphine, the barbiturate abstinence syndrome is a self-limited condition and patients eventually recover (unless they incur a fatal injury during a seizure or die from exhaustion) even though no treatment is given. Ordinarily, the delirium lasts less than five days and ends with a prolonged period of sleep. Clinical recovery appears to be complete and no organic sequelae are known to occur.

Like all other clinical syndromes, abstinence from barbiturates varies in different individuals. Practically all patients who have been consuming large amounts of barbiturates will show anxiety, nervousness, insomnia, tremors and an abnormal electroencephalogram; 75 per cent will have at least one seizure and 60 per cent will become delirious. The least common variation is the development of a delirium without a preceding convulsion.

Individuals who have been ingesting 0.6 gm. or less of barbiturates usually have only minor symptoms on withdrawal. These include nervousness, insomnia and slight tremor. Convulsions are rare and delirium practically never occurs.

Addiction to Other Aliphatic Hypnotics. Addiction to other aliphatic hypnotics such as chloral hydrate and paraldehyde does not constitute a significant problem in the United States. There is relatively little information concerning addiction to these drugs but the few case reports that do exist indicate that the symptomatology of intoxication and withdrawal are probably quite similar to that of addiction to the barbiturates.

Bromides. Chronic intoxication from bromides is apparently a less serious problem at the present time than it has been in the past, probably because of more stringent food and drug regulations which have required the withdrawal of proprietary mixtures containing bromides from the market, and because of the substitution of barbiturates and other drugs for bromides. The clinical picture is that of a slowly developing toxic psychosis which may or may not be accompanied by acneiform eruption. Diagnosis is usually made by finding an elevated blood bromide. A true tolerance to bromides does not occur and there are no abstinence symptoms.

Cocaine. In the United States pure addiction to cocaine is now quite rare. The drug is practically always used in conjunction with either morphine or heroin.[10] Cocaine can be used as a snuff but addicts in the United States usually take cocaine intravenously. The subjective effects produced by intravenous administration of cocaine are very striking—an ecstatic sensation of extreme physical and mental power; sensations of fatigue and hunger are abolished, and psychomotor activity is usually greatly increased. The subjective effects which the addicts value last only a few minutes. They are, however, so attractive that the addict will repeat the dose at intervals of only ten to fifteen minutes in order to recapture the tremendously pleasurable sensations. As the dose is repeated, toxic symptoms appear and increase. These symptoms are referable to stimulation of the central nervous system and to sensitization of the autonomic nervous system. The sympathomimetic signs include elevation of blood pressure, elevation of pulse rate, elevation of respiratory rate, sweating, exopthalmos and mydriasis. Signs of central stimulation include increased deep tendon reflexes, tremors, twitching of muscles, spasms of entire muscle groups and, occasionally, convulsions. A characteristic toxic psychosis, characterized by paranoid delusions, usually develops. The addict feels that people are talking about him and that he is being watched by detectives. Sensations of insects crawling on the skin are very common. Shadows, windowpanes or mirrors may be misinterpreted as being the figure of a detective who is watching the addict. When the toxic

psychosis develops, the cocainist is dangerous and may assault and seriously harm anyone, in the mistaken belief that he is a detective who is persecuting the addict.

Since most addicts in the United States generally push the dose of cocaine to the point described above, intoxication with cocaine in this country is usually acute and not chronic. The experienced addict generally will, on obtaining a supply of cocaine, use it all in a debauch of a few hours. Ordinarily, when toxic symptoms become marked, he will suppress them by taking very large amounts of heroin or morphine intravenously. The more cocaine the addict takes, the more morphine and heroin he needs. Such a process, obviously, cannot be carried out for any extended period of time.

Tolerance to cocaine does not develop; rather, increased sensitivity to the effects of the drug occurs. There are no true withdrawal symptoms.[10]

Sympathomimetic Amines. Certain sympathomimetic amines with powerful central nervous system effects, such as amphetamine (benzedrine®), *d*-amphetamine (dexedrine®) and methamphetamine, are abused by addicts. Usually these drugs are taken orally; only occasionally are they injected. The amounts of drugs used reach enormous levels and addicts are known to take habitually as much as 2,000 mg. of amphetamine daily. Symptoms of intoxication with the sympathomimetic amines resemble those of intoxication with cocaine. The symptoms develop more slowly but persist longer. Sympathomimetic signs, and signs of cortical stimulation are present, and toxic psychoses may occur. Tolerance to these drugs is not usual but may occur[11] and there is no evidence that abstinence syndromes follow withdrawal. The sympathomimetic amines are very seldom used alone. A combination of barbiturates with amphetamine is extremely popular, as is the combination of amphetamine with alcohol.

Mescaline. The use of mescaline is almost entirely culturally determined. The buttons of a small cactus called peyote, which contain mescaline, are used by certain religious cults of Indian tribes in the western and southwestern United States and in Mexico. Ordinarily, the peyote is taken only during religious festivals at certain seasons of the year. The buttons of the cactus are chewed up and swallowed. The effects of peyote are not evident for an hour to an hour and a half after ingestion of the drug; they may last for twelve to eighteen hours. Signs of peyote action include evidence of autonomic stimulation (increased pulse rate, blood pressure, sweating, mydriasis), evidence of marked cortical stimulation (increased tendon reflexes, twitching of muscles) and a toxic psychosis which may resemble various psychiatric entities.[12] Visual hallucinations which include beautiful colors, colored patterns, geometric figures and forms are very common. Feelings of depersonalization and derealization have also been described. As far as is known, no tolerance develops to mescaline and there are no withdrawal signs.

Marihuana. Marihuana consists of the dried leaves of the female hemp plant. In other parts of the world, the resins, which contain the active principles, are concentrated in various ways to form solid cakes of hashish. Hashish may be taken orally in a wide variety of ways or smoked. In the western hemisphere, however, the drug is always smoked. Cigarettes are prepared from the dried leaves which are crushed and screened. Smokers inhale a small amount of smoke and then a large amount of air to dilute the smoke, which is quite irritating. Smoke is held in the lungs as long as possible. The subjective effects include elation, great amusement at simple jokes and distortions in time and space perception. Occasionally, feelings of depersonalization and derealization occur. Overt behavior usually consists of giggling, singing and dancing. Ataxia and dysarthria do not occur. The conjunctivae are reddened and pseudoptosis creates a sleeping appearance. The breath has a characteristic odor, resembling that after smoking cubeb cigarettes; appetite is enhanced and smokers usually sleep more than they normally do. Toxic psychoses may occur in susceptible individuals. No great degree of tolerance is developed and there is no abstinence syndrome.[13]

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Psychiatric Aspects of Drug Addiction*

ABRAHAM WIKLER, M.D. *and* ROBERT W. RASOR, M.D.

Lexington, Kentucky

THE term "drug addiction" refers to a group of behavior patterns which differ from each other in many ways but have as a common characteristic the compulsive use of chemical agents which are harmful to the individual, society or both. It is possible to describe aspects of this group of behavior problems from various sociological, psychologic, physiologic and biochemical points of view, and these are all interrelated because, in the last analysis, the phenomena observed involve the integrated organism in its total environment. However, for present purposes discussion of "drug addiction" will be limited to those aspects of the problem that can be described in "psychodynamic" terms, i.e., by the use of concepts derived from observation of the verbal and nonverbal goal-directed behavior of patients who are or have been addicted to certain drugs. Several alternative formulations of the psychodynamics of drug addiction can be made on the basis of such observations, depending on the "frame of reference" used by the investigator. Their relative validity has not yet been established because of inherent difficulties that beset the solution of many problems in psychiatry, namely, in applying the test of predictive utility to the assessment of the relative importance of various concurrent processes that occur in individuals suffering from the condition under investigation.[1] Therefore it appears desirable to present in this paper, three formulations of the psychiatric aspects of drug addiction and to discuss briefly the kinds of investigation that will be necessary for evaluating the usefulness of each approach.

A SYMPTOMATOLOGICAL FORMULATION

Study of life histories in a large number of former narcotic addicts confined to institutions has indicated that, in the majority, behavior deviations are demonstrable which may be described as "neurotic" or "psychopathic." In a small number, chronic painful illnesses appeared to alter the course of an otherwise "normal" existence, and in a similarly small group frankly psychotic behavior was associated with the habitual use of opiate drugs.[2–4] In each group the use of chemical agents appears to serve somewhat different purposes. "Neurotic" individuals presumably seek relief from "anxiety" ("negative euphoria") while "psychopaths" are prone to use drugs for the purpose of creating a state of elation ("positive euphoria"). In "normal" individuals addiction to narcotics appears to be related to the need to relieve pain, while in "psychotic" individuals such agents may be used to relieve depressive feelings.[5] From this point of view opiates and their analogs, marihuana, cocaine, barbiturates and alcohol, are equivalent with respect to the purposes served by the use of chemical agents except that repeated, regular use of some (e.g., opiate-like drugs and barbiturates) produces "physical dependence." The development of the latter is viewed as a complicating process, altogether undesirable from the standpoint of the user, but not as an essential feature of drug addiction. With the development of "physical dependence" the "euphoric" effects of such agents become more difficult of attainment, and drugs are then used almost solely for the purpose of preventing distressing "abstinence" phenomena. In this formulation relapse to the use of drugs is related entirely to the personality defects of "neurotic," "psychopathic" or "psychotic" individuals, or to recurrence of intractable pain in "normal" persons.

A PSYCHOANALYTIC FORMULATION

Study of drug addicts by the use of psychoanalytic technics (usually after withdrawal of drugs has been accomplished) enables one to formulate the drug addiction process in terms of concepts derived from "transference" and other phenomena that occur in the special

* From the National Institute of Mental Health Addiction Research Center and the Clinical Division, Public Health Service Hospital, Lexington, Ky.

relationship that develops between the patient and the analyst. Such investigations[6–9] indicate that many drug addicts are individuals whose psychosexual development has been arrested at, or has undergone regression to, infantile or even to more primitive levels. In infancy and early childhood a strong, consistent father figure has generally been lacking, whereas the mother has been overindulgent and rejecting in an inconsistent way. As a consequence of such experiences the child has been unable to learn that all his wants cannot be fulfilled in reality and has come to regard other persons, particularly the mother, or substitutes for her, merely as objects to be used in self-gratification ("narcissism"). Because of arrest in psychosexual maturation, "oral" cravings become paramount whereas genital pleasures become devoid of interest. Since, in reality such wants can never be fulfilled, frustration results and the narcissistic, oral-dependent individual reacts with hostility, often toward the mother or other women. Such hostility may be turned inward on the self, resulting in self-destructive wishes. The use of chemical agents by these individuals serves a number of purposes. The sense of frustration is relieved by the induction of euphoria, consequent to distortion of "reality" by the pharmacologic actions of drugs. Since the use of drugs for such purposes is condemned in our culture, the very act constitutes an expression of hostility, and since this practice eventually entails disastrous consequences, it achieves a measure of self-destruction and expiates guilt simultaneously. In addition, other psychodynamic processes appear to play a role in the genesis of drug addiction. The narcissistic individual is peculiarly prone to experience impairment of self-esteem and, because of this and his hostile impulses, depressive moods occur frequently and they are relieved by the use of drugs. Also, such persons may seek to demonstrate their "masculinity" by hard drinking, or intense orgastic experiences may be achieved by injection of opiates (intravenously), serving as a passive substitute for genital satisfactions. In addition, the self-administration of drugs, particularly by the parenteral route, is associated with erotic fantasies of various sorts—masturbatory, incestual, castrative, etc., of a highly symbolic nature. According to this formulation, " . . . not the toxic agent, but the impulse to use it, makes an addict of a given individual."[6] The particular agent used is not regarded as of prime importance, emphasis being laid more on the "distortion of the perception of reality" which such drugs produce and their forbidden status in our society. The predisposition to use drugs is considered to exist prior to experience with drugs. The repetitive use of such agents is ascribed to the predisposition itself and the contrast between the elated state produced by drugs and the disillusionment which ensues when such effects wear off. Likewise, the notorious tendency of drug addicts to relapse is related to the basic personality defects of the individual.

A PHARMACODYNAMIC FORMULATION

An hypothesis which differs from the foregoing in a number of ways can be made on the basis of data acquired by detailed interrogation of former narcotic addicts concerning the effects of various drugs in a variety of actual life situations and the observation of changes in behavior which such subjects exhibit during experimental re-addiction to opiates, barbiturates or alcohol, in a standardized setting.[10,11] Such data indicate that what the addict means by stating that he feels "unusually well" ("euphoria") varies considerably in different types of drug addiction. In amounts preferred by such individuals all of these agents produce marked changes in the pattern of affective behavior. This alone is often adduced by the subjects as a reason for using drugs: "to get me off the natural," and indicates that under ordinary circumstances the prevailing mood of such individuals is dysphoric or perhaps anhedonic. However, former narcotic addicts express strong preferences for opiates although, if these are not available to them, they will volunteer for studies on barbiturates or alcohol with some reluctance. Explanations for such preferences vary. For example, some state that alcohol upsets their stomachs; others object to alcoholic "hangovers" but, in many instances, preference for opiates is related by subjects to effects peculiar to these agents which differ sharply from the effects of barbiturates or alcohol. The general tenor of their attempts to explain such contrasting effects may be expressed in the form "Drugs (i.e., opiates) make me satisfied; alcohol makes me want to go out and get satisfied." On further interrogation, the majority of such individuals explain that in ordinary life situations opiates (usually heroin or morphine) reduce appetite, pain and erotic urges of all sorts, heterosexual,

homosexual or autoerotic. In addition, intravenous injection of these agents produces a transient "thrill" akin to sexual orgasm, except that it is centered in the abdomen. After these effects have developed a sense of gratification or satisfaction is achieved and they feel more "at ease" and free to do what they "want to do." In some situations they may "want" to doze peacefully and enjoy daydreams of wealth, power or social prestige. In other situations they may "want" to socialize, and they feel more comfortable in the presence of women. Furthermore, some opiate users state that these agents do not impair, others state that they actually improve, their ability to do useful work and that under the influence of opiates, they are less aggressive and "keep out of trouble." On the other hand, they state that when they are under the influence of intoxicating doses of barbiturates or alcohol, erotic urges of all sorts are enhanced, judgment capacity for useful work is impaired, and they are frequently involved in fights, sexual excesses or other types of aggressive behavior.

It is difficult, of course, to verify statements such as these relative to the contrasting effects of drugs in actual life situations. However, observations made under experimental conditions are in substantial agreement with them. Thus, as long as adequate amounts of opiates are administered, aggressive, antisocial behavior is practically never observed, personal hygiene is maintained, assigned responsibilities are discharged satisfactorily, psychologic tests of performance reveal little or no impairment, and the sensorium remains quite clear, while anxiety associated with anticipation of pain is reduced. Striking, also, is the fact that "anosognosia," or the denial of illness or realistic sources of anxiety, cannot be demonstrated ordinarily. In contrast, former opiate addicts who are receiving intoxicating doses of barbiturates tend to become untidy, surly, hostile or pugnacious, engage openly in such sexual activity as is possible in this particular situation, and they either deny or rationalize obvious sources of anxiety or evidence of gross functional impairment, such as dulling of the sensorium, ataxia, dysarthria, etc. The behavior of former narcotic addicts who are receiving intoxicating doses of alcohol is quite similar. Affective behavior is characterized by marked intensity and lability, and may assume different forms—affectionate, hostile or sexually aggressive—depending on the nature of the stimuli to which the subject is exposed.

It may be inferred, therefore, that different classes of drugs alter patterns of behavior in different ways, through different effects on motivations of a "primary" and "secondary" nature.[10] Also, the use of drugs of one type or another appears to represent an attempt at self-therapy, although other processes, such as the indirect expression of hostility by engaging in a socially condemned activity, or the need to identify with a particular social group, may reinforce the motivation to experience drug effects. The choice of a particular class of drugs may be explained on the basis of the assumption that a given agent facilitates or hinders specific patterns of behavior which are acceptable to the user. Thus former narcotic addicts, regardless of conventional "personality" classifications which may be applied to them, are individuals in whom the chief sources of anxiety are related to pain, sexuality and the expression of aggression. Also, they are generally non-competitive persons who prefer to handle such anxieties by avoiding situations which provoke them and who are prone to "talk" their way out of threatening situations rather than to solve such problems by aggressive acts. Recent studies[12] indicate that juvenile narcotic addicts display much the same sort of behavior, and it may be inferred that the well known fact that narcotic drug addiction often begins in adolescence is related to the intensity of conflicts in the areas of sexuality and assumption of aggressive masculine roles which exist during this period. Comparable studies on chronic alcoholics have not yet been made with reference to personality traits that may be expected on the basis of the present hypothesis. It may be predicted that in such individuals a greater variety of anxiety-provoking conflicts and a greater tendency to "act out" such problems will be found.

It will be noted that according to this formulation no pre-addiction "impulse" to use drugs is postulated. As a matter of fact, introduction to the use of drugs is usually quite accidental, and the first or second drug experiences are often unpleasant. Whether or not the user experiences "euphoria" appears to depend to a great extent on the situation which exists at the time that drugs are used. The precise nature of the requisite "situation" has not yet been fully elucidated but on the basis of the present hypothesis it may be inferred that the

degree of "euphoria" which a given drug produces is related directly to the intensity of the needs which the agent in question satisfies specifically. However, in the case of opiates, at least, such drug actions are diphasic in character. The gratification of certain needs is followed by their intensification after the initial effects of the drug have worn off. The initial "euphoria" can be reestablished by a second dose but the same cycle of events occurs. Furthermore, tolerance and a new pharmacogenic need for the agent develops after repeated use of an opiate drug, which become apparent in the form of "abstinence phenomena" when opiates are withheld. Recent studies[13,14] have shown that the processes responsible for such "pharmacologic dependence" develop very early, perhaps after a few "therapeutic" doses of morphine, methadone or heroin, and that this process is related, at least in part, to factors of little or no symbolic significance. Thus the self-perpetuating character of opiate drug use is related directly to the pharmacologic properties of these agents. Quite likely, this is true also of barbiturates and alcohol although further demonstration of such processes is necessary.

In the case of opiate addiction the pharmacogenic need for such drugs which develops in the course of addiction is not altogether unpleasant. While the original satisfactions experienced by the use of opiates diminish progressively as tolerance develops, a new source of gratification is derived from the repeated relief of craving for these drugs which is an integral part of the "abstinence phenomena." Also, it appears that no tolerance develops to the orgastic effects which are experienced by injecting such agents intravenously. Hence, "getting hooked" on opiates is quite attractive to some addicts. In fact, it may be more than a coincidence that the drug which most addicts prefer, namely, heroin, produces the most intense degree of pharmacolgic dependence. Nevertheless, this process ultimately produces changes in the addict's behavior that are disastrous for him. The original "euphoric" effects become more and more difficult of attainment, and progressively increasing amounts of opiates are needed to satisfy pharmacologic dependence. Eventually, the motivation to obtain sufficient supplies of the drug becomes paramount, relegating all other motivations to positions of minor importance. Antisocial behavior may be displayed under such conditions when opiates are not obtainable, or the desperate addict may use large quantities of barbiturates or alcohol as a substitute, with no success, but with complications resulting from the use of such intoxicants. Sooner or later the addict will be forced to seek treatment, either because of legal-economic factors, decline in social productivity, disruption of family ties, or the appearance of disease processes that have been masked by the analgesic actions of opiates. In the case of barbiturate or alcohol addiction disastrous complications are even more serious. Self-injury due to mental confusion or involvement in fights, disintegration of personal relationships in family, business or professional life, legal difficulties because of the increased tendency to "act-out" in socially unacceptable ways and disease processes due to avitaminosis are added to pharmacologic dependence and make the necessity for treatment even more urgent than in the case of the opiate addict.

The withdrawal phenomena associated with drug addictions may serve a variety of psychologic purposes. Certainly they are not deterrents against relapse. The "cold turkey" treatment has been widely employed in penal institutions, yet this procedure has produced no perceptible reduction in the rates of admission to these facilities. In many cases it is possible to demonstrate that the suffering associated with the abstinence syndrome serves the addict as a means of expiating guilt and leaves him free to relapse because he has paid his "debt to society." On the other hand, the almost instantaneous relief which opiates afford for such suffering serves to heighten the addict's esteem for this class of drugs. This may also be true with respect to barbiturates and alcohol in addictions to these agents.

Very likely, such factors contribute in an important way to the well known propensity of addicts to relapse after "cures." Also, a "conditioning" process may play a role in relapse, particularly in the case of addiction to opiate drugs. A number of opiate addicts have stated that experiences akin to that of the opiate abstinence syndrome, including intensified "craving" for such drugs, may occur long after "cure," when opportunities to obtain narcotics present themselves. Analogous phenomena have actually been observed in the course of research on former opiate addicts waiting for the beginning of an addiction study. Such a "conditioning" process has been formulated theoretically[15] and

is currently under investigation. In addition to these factors and those that contributed to the genesis of the addict's first addiction, the changed social standing of the former addict contributes to relapse, for in our culture such individuals are often rejected by society and they can find acceptance only by association with other addicts or former addicts.

PROBLEMS FOR FUTURE RESEARCH

The three formulations presented overlap in some areas and diverge in others. They are not mutually exclusive, for it is to be expected that no single "frame of reference" will suffice to explain all aspects of any form of human behavior.[16,17] However, the usefulness of each hypothesis in predicting observable events (in this instance, the compulsive use of drugs of one sort or another) remains to be tested. This can be accomplished best by a *comparative* study of the personalities of *young* individuals and their families (particularly their mothers) in a given cultural milieu. The subjects to be studied should include comparable groups of (1) non-users of drugs; (2) those who have been introduced to drugs but have not continued to use these agents; (3) those who have been introduced to opiates, marihuana, cocaine, barbiturates and alcohol but have continued to use one type of drug only; (4) those who have used all types of drugs continually, without discrimination. In these individuals "personalities" should be studied from each of the standpoints delineated in this paper, with a view toward determining whether correlations can be made between any type of personality and the subsequent development of addiction to drugs of a particular type, using non-users of drugs as controls. Furthermore, it will be necessary to observe the social productivity of drug users of all sorts, as well as that of non-users, in their ordinary social settings during development of addiction, after "cure" and during relapse. In addition, it will be necessary to assess prevailing cultural standards with respect to values set on passive, competitive and aggressive behavior, attitudes toward particular types of drug addiction, conformity or non-conformity, etc. Certain difficulties in carrying out such a study can be foreseen. For example, the very act of "examining" potential drug addicts may modify their "personalities," and the introduction of a team of psychiatrists, psychologists and social workers may alter the immediate environment which is to be investigated. However, such difficulties are inherent in all scientific investigations and always limit the extent to which one may apply inferences derived from such studies. Nevertheless, significant results can be expected from such an undertaking and will undoubtedly aid in verifying or modifying the hypotheses presented, or furnish data from which more useful formulations can be made.

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Treatment of Drug Addiction*

H. F. Fraser, M.D. *and* James A. Grider, Jr., M.D.
Lexington, Kentucky

This discussion will be limited to the treatment of patients addicted to natural and synthetic narcotics, cocaine, marihuana and barbiturates. Although addiction to alcohol constitutes the greatest single addiction problem in most of the world, it will not be discussed since a separate treatise would be required for alcohol alone. For convenience of presentation treatment of addiction will be discussed under three phases, (1) outpatient or office management, (2) withdrawal of drugs and (3) rehabilitative and psychiatric treatment.

OUTPATIENT MANAGEMENT

Office Handling of Narcotic Addicts. A comprehensive procedure for the physician to follow when an addict appears in his office has been described recently in the Journal of the American Medical Association.[1] First, the physician must be familiar with the Federal Narcotic Laws and Regulations. The addicting drugs which are controlled by the Harrison Narcotic Act include opium, morphine, heroin, dihydromorphinone (dilaudid®), methyl-dihydromorphinone (metopon®), 3-hydroxy-N-methylmorphinan (dromoran®), codeine, dihydrocodeinone (hycodan®), meperidine (demerol®), methadone (dolophine®), and cocaine. Marihuana is controlled separately by the Marihuana Tax Act. The United States Bureau of Narcotics has interpreted the Harrison Narcotic Act, insofar as it affects physicians and pharmacists, in Pamphlet No. 56, "Prescribing and Dispensing of Narcotics under the Harrison Narcotic Law." The most pertinent provision of the narcotic regulations respecting addiction reads in part as follows: "An order purporting to be a prescription issued to an addict or habitual user of narcotics, not in the course of professional treatment, but for the purpose of providing the user with sufficient narcotics to keep him comfortable is not a prescription within the meaning and intent of the act; and the person filling such an order, as well as the person issuing it, may be charged with violation of the law." In addition to federal laws there are state laws with which the physician must familiarize himself but, in general, the physician will be acting in accordance with the consensus of medical opinion with regard to addiction and will be complying with the letter and spirit of both federal and state laws if he follows two principles set forth by the House of Delegates of the American Medical Association: (1) Ambulatory treatment of narcotic addicts should not be attempted as institutional treatment is always required; (2) narcotic drugs should never be given to an addict for self-administration.

The physician should realize that treatment of drug addiction of any type is primarily a psychiatric problem and favorable results cannot be anticipated unless treatment has been continued for several months. Attempts to carry out such therapy in the home or office fail almost invariably.

When the patient has agreed to go to an institution for treatment and has presented satisfactory evidence that he has taken steps to obtain admission, the physician may then administer narcotics in minimal doses but only for the minimal period of time necessary for the patient to complete arrangements for institutional treatment. Drugs must be administered by the physician or, if the patient is in a hospital, by nurses on proper written orders. Drugs, or prescriptions for drugs, must never be given to the patient for self-administration. It is advisable to limit the initial dose to 16 mg. (¼ gr.) of morphine or 10 mg. (⅙ gr.) of methadone. It practically never should be necessary to exceed as a single dose 60 mg. (1 gr.) of morphine or 30 mg. (12 gr.) of methadone.[1] The type of drug administered and the dose should be unknown to the addict and every precaution should be taken to prevent

* From the National Institute of Mental Health, Addiction Research Center and the Clinical Division, Public Health Service Hospital, Lexington, Ky.

the addict from obtaining narcotics from other sources.

The narcotic laws do not, of course, prohibit the use of opiates in patients suffering from advanced carcinoma, tuberculosis or other chronic painful diseases. In such cases the physician is concerned primarily with relieving suffering and only secondarily with addiction. Nevertheless, ethical medical practice demands that certain principles be followed: (1) The physician prescribing narcotics for such patients should be personally attending them; (2) the diagnosis of a painful, incurable disease should be confirmed by consultation; (3) all means for relieving pain other than narcotics should be exhausted and (4) narcotics should not be given to the patient for self-medication.

While it is known that it is practically impossible for addicts in advanced states of tolerance to take a lethal dose of narcotics, addicts who have lost their tolerance may take a fatal dose. N-allylnormorphine (nalline®), a chemical analogue of morphine, is a specific antidote and in these cases it should be administered intravenously in a dose of 5 to 20 mg.[2,3]

Office Treatment of Barbiturate Addicts. The Harrison Narcotic Act does not apply to barbiturates, which are controlled by state laws and by the Federal Food and Drug Law.

When barbiturates are administered in the usual therapeutic doses under supervision of a physician, addiction does not occur even though the drugs may be taken for many months. However, chronic consumption of large amounts of barbiturates results in true addiction.[4] Abrupt withdrawal of barbiturates from persons who have been consuming 0.8 gram or more of these drugs daily may provoke a serious abstinence syndrome characterized by convulsions and delirium.

Institutional treatment of barbiturate addiction is just as necessary as it is in narcotic addiction. The physician should refuse to prescribe barbiturates for a person he believes is addicted to them until the patient agrees to institutional treatment and he should not continue to prescribe these drugs if the patient procrastinates and does not promptly complete arrangements for institutional treatment.

Selection of an Institution for Treatment. When the diagnosis of addiction has been made and the patient has agreed to go to an institution for treatment, the next step is the choice of the institution. The selection will depend upon the type of case, the financial situation of the patient and other factors. Many private sanitoriums make a specialty of treating various kinds of addiction. Advice regarding these private institutions may be obtained from local medical societies or from the American Medical Association. If the addict is unable to pay for treatment, local or state facilities may be available. Advice concerning these can be obtained from City and State Health Departments. If no such facilities are available, the patient may be referred to one of the two Federal Hospitals that treat narcotic addiction, the U. S. Public Health Service Hospitals located in Lexington, Kentucky and Fort Worth, Texas. Communications respecting admission may be directed to the Medical Officer in Charge of either hospital. Patients addicted to opiates, synthetic analgesics, marihuana and cocaine are eligible for admission to these institutions. Patients addicted to alcohol and barbiturates are not eligible for admission to these Federal Hospitals unless they are concurrently addicted to narcotic drugs. If the patient is indigent, there is no charge for treatment; but if the patient has funds, there is a charge of $5.00 per day. The hospital in Lexington accepts both men and women but in the Fort Worth hospital only males are admitted.

The physician should explain to the patient that withdrawal from drugs is an unpleasant but not a dangerous procedure, and that the patient should cooperate with the institution until the full program of treatment is completed. Although physical dependence on drugs may be relieved in two weeks, psychic dependence and a poor physical condition persist, so patients are requested to remain a minimum of 135 days in these hospitals.

WITHDRAWAL OF DRUGS

Opiates. Although a great many withdrawal procedures have been published,[5–7] the best method of withdrawing heroin, morphine or similar drugs from addicted patients involves substitution of methadone for whatever opiate or synthetic analgesic the patient has been using, followed by reduction of the dosage of methadone over a period of about ten days. This method of treatment is based on the facts that methadone will prevent the appearance of signs of abstinence from any known analgesic drug and that abstinence from methadone is milder than abstinence from any of the other commonly used analgesics. One milligram of

methadone can be substituted for 4 mg. of morphine, 2 mg. of heroin, 1 mg. of dilaudid, or 20 to 30 mg. of either meperidine (demerol) or codeine.

The speed with which withdrawal is completed is dependent on the physical condition of the patient and the extent to which he is dependent on narcotics. Addicted patients with serious organic disease should not be subjected to the strain of relatively rapid withdrawal. In such cases it is best to treat the organic disease before attempting to treat the addiction. When, in the judgment of the physician, the organic disease has improved to the point where mild abstinence carries no danger, withdrawal is cautiously begun and, depending on the patient's response, withdrawal is completed in fourteen to thirty days. In the experience at the Lexington Hospital less than ½ of 1 per cent of narcotic addicts require such special treatment.

The first decision which must be reached before withdrawal begins is the degree of dependence on narcotics. The patient's history is of little use in this connection since addicts frequently exaggerate the quantities of drugs taken in the hope of receiving large amounts of narcotics in the first part of withdrawal. Furthermore, illegal drugs, especially heroin, are adulterated and the narcotic concentration may vary enormously. Hence the patient, unless he has had considerable experience with various narcotics, is unable to estimate the quantity of narcotics used.

The degree of dependence is best estimated by the physical examination, which will disclose whether the patient is intoxicated with narcotics or is exhibiting symptoms of abstinence.[7,8] If a patient shows morphine-like intoxication, or if he displays no signs of abstinence, narcotics should not be administered until definite symptoms of abstinence appear. When symptoms of abstinence are present on admission or develop shortly afterward, it is usually possible to estimate the addiction dosage, especially if the physical findings are considered in conjunction with the addiction history. Information regarding the specific drug and the number of hours which have elapsed since the last dose of self-administered narcotics is very helpful in this connection.

During the first two days of hospitalization the dose of methadone should be sufficient to control nearly all symptoms of abstinence. By this method the patient will be able to eat, become oriented to the hospital regimen and psychiatric rapport may be established with the physician. During this interval routine laboratory work, roentgenograms and physical examination should be completed. Depending on the severity of abstinence, a dose range of 5 to 40 mg. of methadone three times daily is usually sufficient to prevent the appearance of abstinence signs, regardless of the amount or the drugs the patient has been using. Reduction is started after two days by cutting the dosage of methadone by 50 per cent. This level should be maintained for about two days, after which the dose is reduced at approximately two-day intervals to 30, 10 and 5 per cent of the amount of methadone which just prevented the appearance of abstinence in the initial phase of treatment. As the end of withdrawal approaches both the amount and frequency of medication should be reduced. If the degree of physical dependence is not great, withdrawal may be completed in five to seven days and, in some cases, even less time may be required.

While narcotics are being withdrawn all addicts require reassurance; they should be examined daily for withdrawal signs so that appropriate changes in the treatment schedule may be made.

No special dietary measures are necessary during withdrawal unless the presence of an organic disease requires a special diet. Fruit juices and other attractive drinks should be available during the first four or five days. Anorexia is very common during withdrawal but a return of appetite is spontaneous and rapid.

Insomnia is conspicuous during withdrawal. After three to five days it is advisable to give 0.1 to 0.2 gm. of pentobarbital or a similar hypnotic at bedtime, but the use of sedatives should not be continued for more than a few nights.

It is not advisable to permit visitors during this phase of treatment since the addict may be depressed, his craving for narcotics has not diminished and he may attempt to have relatives or friends smuggle drugs to him. Furthermore, addicts receiving narcotic drugs should be segregated from other addicts who are in the rehabilitative phase of treatment. Observing other patients receiving narcotics creates a situation which is favorable for developing an intensified craving for morphine.

Cocaine and Marihuana. Since no physical

dependence is produced by cocaine or marihuana, withdrawal should be abrupt and complete and no substitution therapy is necessary. Insomnia and irritability should be treated with sedatives.

Barbiturates. Isbell[9] has emphasized that barbiturates should be withdrawn very slowly and cautiously from barbiturate addicts. As in the case of morphine addicts, statements of the barbiturate addict regarding daily intake may be very unreliable. Patients showing barbiturate intoxication[4,10] on admission should not be given additional sedatives until signs of intoxication have become mild. Patients who show signs of mild barbiturate abstinence on admission such as anxiety, weakness, nausea and tremor are in danger of developing convulsions and/or psychosis.[4,10] Such cases should be given 0.2 to 0.5 gm. (3 to 6 gr.) of pentobarbital (nembutal®) orally or parentally at once. If symptoms are not relieved after one hour, the dose should be repeated.

After symptoms of intoxication have become mild, or after early withdrawal symptoms have been brought under control, the patient should be given barbiturates orally four times daily. The dosage of barbiturates should be adjusted to that which just maintains a mild degree of intoxication. Ordinarily 0.2 to 0.4 gm. of pentobarbital four times daily will suffice for this purpose.

After the patient has been observed for a day or two, reduction of barbiturates can be started. The dosage should not be reduced more than 0.1 gm. (1½ gr.) daily. If the patient has been taking 1.0 or more gm. daily, the total withdrawal period should extend over a period of three or four weeks.[11] If the patient becomes nervous, apprehensive and weak, or if paroxysmal high voltage spike and dome waves appear in the electroencephalogram, the reduction should be stopped until these signs have cleared.

Patients being withdrawn from barbiturates must be kept under close observation. Their beds should be provided with sideboards or else their bed should be a mattress on the floor so that if convulsions occur they will not fall to the floor. Patients should not attempt to walk, bathe or go to the bathroom unattended. Diet should be light during the first few days but subsequently no restrictions are necessary.

The diagnosis of barbiturate addiction should always be borne in mind in patients who suddenly develop convulsions and/or a toxic psychosis. If such cases are not recognized and properly treated, a fatal result may ensue.[12,13] If after complete examination of such cases the diagnosis of abstinence from barbiturates seems likely, appropriate treatment consists of rapid reintoxication with barbiturates which may be given intramuscularly or intravenously if necessary. This program will arrest further convulsions but it may not completely control the toxic psychosis.[13] Prompt administration of *sufficient* barbiturates will control excessive hyperactivity during the delirium and prevent exhaustion.

Delirious patients must be under continuous observation, rectal temperature checked three times daily and adequate fluid and food intake maintained. Fever of more than 104°F. is a serious sign[12,13] and should be combatted by measures which favor body heat loss, such as keeping the room cool, the patient uncovered and administration of antipyretics. "Cold packs" should be avoided since these place undue strain on an already impaired circulatory mechanism.[12,13] Once improvement is noted withdrawal is accomplished by gradual reduction of barbiturates as described previously.

It should be remembered that acute barbiturate intoxication may be superimposed on chronic barbiturate intoxication. Patients who are chronically intoxicated with barbiturates may become confused and ingest such large amounts of barbiturates that serious acute poisoning develops. Whenever a patient who has been acutely poisoned with barbiturates recovers from coma, every effort should be made to ascertain if he has been taking large doses of barbiturates daily and, if so, he should be mildly reintoxicated with barbiturates and then gradual reduction begun as described above.

Combined barbiturate and opiate addiction has become quite common. Withdrawal of both drugs can proceed concurrently with more time usually being required to withdraw barbiturates than opiates.

REHABILITATIVE AND PSYCHIATRIC TREATMENT

Following the withdrawal of opiates and/or barbiturates rehabilitative and psychiatric treatments are instituted.

Residual symptoms of abstinence from drugs, such as feelings of weakness, varying degrees of insomnia and anorexia may persist for several weeks but "the physician must adopt a reassur-

ing but uncompromising attitude." Opiates and barbiturates must not be indulged in once the withdrawal period is completed. Intercurrent physical illnesses are handled in the same manner as they would be in a non-addict patient. If surgical procedures are required in an addict who has been withdrawn from drugs, opiates and barbiturates are administered preoperatively and postoperatively in the same dosages as would be given to a non-addict. Once the acute phase of illness has passed, opiates and barbiturates must be rapidly eliminated.

General rehabilitative measures consist of dietary, vocational, recreational and social procedures.

Malnutrition is a common condition of addicted patients. But once drugs have been withdrawn recovery of appetite is spontaneous and a good general diet will rapidly improve the nutritional status. Gastrointestinal complaints often may be ameliorated by ancillary psychiatric measures after ruling out organic diseases. Often, symptoms suggestive of visceral disease are not confirmed and they may subside as the patient's adjustment within the hospital improves.

Vocational therapy plays an important part in the rehabilitation of the addict. A large percentage of addicts have not developed a satisfactory work pattern. Mere assignment of a job to an addict patient carries little hope of permanent occupational adjustment. Nevertheless a job of some kind within the institutional setting is necessary to occupy part of the patient's time. In the younger addicts particularly, a profitable and interesting vocational assignment, leading to some specialized skill, may prove very helpful. A well rounded school program, which functions at all educational levels, is a valuable supplement to vocational treatment. Complete vocational rehabilitation requires that during hospitalization plans should be made for finding the patient a suitable job in the community to which he returns. Such job placement may prove difficult because of social ostracism of former addicts.

The inadequate recreational and social life of many addict patients reflects a further deficiency in their adjustment to our cultural environment; just as the addict frequently has not learned to work, neither has he learned to play. Recreational measures should be more than a matter of physical exercise and should teach socialization and group participation as well. For these reasons the recreational program should be diversified and include organized sports, motion pictures, shows directed and staged by patients, a library and facilities for playing indoor games, cards, etc.

The above general rehabilitative measures are only supportive. Psychologic treatment directed toward the patient's personality needs is necessary if any permanent success is to be expected. These include participation in "Addict Anonymous" (based on the principles of Alcoholics Anonymous), group psychotherapy and individual psychiatric treatment with a complete follow-up of the patient to his own community. In addition, where specifically indicated, such physical forms of psychiatric treatment as electroshock therapy, insulin shock, lobotomy, etc., may be used provided the severity and specificity of the emotional illness warrants this; but it must be emphasized that these more radical measures are of no value in the treatment of drug addiction *per se*.

Addict Anonymous was first organized by the patients at the Public Health Service Hospital in Lexington, Kentucky. Participation in this program yields a type of mutual support and acceptance that some addicts are able to utilize whereas insight psychotherapy may be unacceptable. It has been the experience of the Lexington Hospital that Addict Anonymous has contributed significantly to better institutional adjustment. Many discharged addicts later identify themselves with their local "chapter" of Alcoholic or Addict Anonymous.

Group therapy has been used in this institution on a trial basis. As with other types of treatment of addiction, the effectiveness of group therapy is difficult to evaluate since follow-up studies to determine the incidence of relapse in any specially treated group as compared to a group given routine treatment are very difficult to carry out. However, mutual discussion of emotional problems and social participation with other patients would seem partially to fulfill some of the obvious needs of the poorly motivated addict.

Individual treatment of the addict is a challenging problem. Many addicts deny any need of psychiatric assistance and many frankly refuse therapy. The drug addict has "found something"—morphine—which allays his vague free-floating anxiety. To demand of him that he relinquish a tested product for the relatively unpredictable success of psychotherapy is to

demand more than many addicts can give. In older addicts frequently patterns of dependence, aggressiveness, passivity and other faulty adjustments have been so firmly established that significant changes in personality structure are not to be expected. However, there are many patients who have sufficient awareness of their anxiety to recognize the need for psychiatric help. As with the alcoholic, psychiatric success is difficult to evaluate and actual cure is regarded by some as unobtainable. Nevertheless, some of these patients are helped. "As with the chronic alcoholics many relapses may be followed by a permanent cure."

If individual psychiatric therapy is to be administered it is necessary to evaluate the therapeutic prognosis of individual patients by medical, psychiatric and psychologic measurements so that patients potentially amenable to psychiatric therapy can be selected. Such measurements would eliminate the aged and chronically ill patients, the physically healthy addicts who have repeatedly resorted to drugs for the solution of their emotional problems, and the severely disturbed neurotics or psychotics who may defy treatment whether or not they are addicts. Experience indicates that psychiatric treatment should be directed toward young patients with relatively well developed ego strengths who express, or are capable of expressing, overt anxiety and whose strivings and goals show good contact with reality and awareness of social and cultural demands. The merits of psychoanalytical or non-analytical treatment will not be argued here. Whatever type of psychotherapy is given should be individualized and administered at regular intervals over a prolonged period. Although continuation of psychotherapy after discharge may be difficult, every effort should be made to provide the patient with psychiatric treatment in the community to which he returns.

Prognosis. The use of addicting drugs to the point of physical dependence does not necessarily produce a habitual life-long addict. Social and environmental pressures may lead to a state of addiction but once satisfactory treatment has been carried out the patient may find, either individually or through psychotherapy, ways of handling tensions and anxieties without resorting to drugs. Data are available that indicate that a fair percentage of addicts are able to abstain from the use of drugs for prolonged periods and, in some instances, permanently. Pescor,[14] in a follow-up study of 4,766 male patients discharged from the Lexington hospital between January 1, 1936, and December 30, 1940, found that the status of 39.6 per cent was unknown, 7 per cent had died, 39.9 per cent were known to have relapsed to the use of drugs while 13.5 per cent were known to have remained abstinent for at least three years. Vogel[15] stated that up to January 1, 1948, 11,041 patients had been admitted to this hospital. Of these 61.4 per cent had been admitted only once, 25.6 per cent twice, 6 per cent three times, 2.9 per cent four times and 3.8 per cent five times or more. His report also showed that 54 per cent of discharged male patients and 61.9 per cent of discharged female patients had not been reported to have been admitted to any correctional institution or held for any law violation. Nemec[16] currently reports that since the opening of the Public Health Service Hospital in 1935 at Lexington, Kentucky, a total of 18,699 patients had been admitted through June 30, 1952. Of this number 12,005 or 64 per cent were first admissions only; 4,004 or 21 per cent were second admissions; 1,170 or 6 per cent were third admissions, while all other patients with four or more admissions comprised the remaining 9 per cent.

Although there are no statistics available on the prognosis of barbiturate addiction, there is no reason to suppose that the outlook is more favorable than in narcotic addiction or alcoholism.

Even though an addict may return to the use of drugs, hope should not be abandoned. Although the prognosis becomes worse with each relapse, cases are known that have abstained permanently after several relapses. Also, addicts, even though they do relapse, are frequently productive and socially useful during periods of abstinence between addictions. This definitely represents a considerable gain and makes further treatment worth while.

Prevention of Drug Addiction. The prevention of addiction would seem to depend on (1) control of the source and supervision of the dispensing of addicting drugs; (2) prompt and satisfactory treatment of addicts and (3) a well directed mental health and education program.

The legal control of all sources of narcotics and barbiturates is one effective prophylactic measure available.[17,18] For example, during the last world war, when smuggling of contraband narcotics was at a minimum, the census at the Lexington hospital was significantly reduced.

In the United States the highest occupational incidence of narcotic addiction is among physicians and nurses, those having the greatest accessibility to narcotics.

Prompt treatment of all addicts is, of course, indispensable since each addict is a potential source for extension of addiction. For example, it is well known that if one spouse is an addict the other spouse is much more apt to become addicted.

In the United States mental health and educational programs are now being employed more extensively and, after several years, we may be able to better evaluate their effectiveness in reducing addiction.

The physician should avoid prescribing barbiturates *continuously* for relief of nervousness and insomnia, especially in neurotic patients or those with a history of alcoholism, because such patients are prone to take drugs in excess and so become addicted. Likewise, caution is in order when administering narcotics to this class of patients.[19]

The physician should also employ the same care in the prescription and administration of any of the new synthetic analgesics that he knows to be applicable to the use of morphine. All of these substances (methadone,® dromoran,® nisentil,® etc.) have morphine-like properties, have proven addiction liability and are subject to the same restrictions as morphine and its derivatives.

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History and Mechanism of International and National Control of Drugs of Addiction

ALFRED L. TENNYSON, LL. B.
Washington, D. C.

THE conference of the International Opium Commission which convened in Shanghai in February, 1909, on the initiative of the United States Government marks the first effective effort toward securing international action to control the traffic in opium and the dangerous drugs obtained therefrom. One of the recommendations of the Commission was that drastic measures be taken by each government in its own territories and possessions to control the manufacture, sale and distribution of morphine, and of such other derivatives of opium "as may appear on scientific inquiry to be liable to similar abuse and productive of like ill effects." Three years later representatives of twelve world powers, including the United States, met at The Hague to formulate the recommendations of the Commission into an international convention. From this meeting came the first important international agreement on the subject, the International Opium Convention of 1912.

THE INTERNATIONAL OPIUM CONVENTION OF 1912

This Convention, informally referred to as the Hague Convention of 1912, was designed "to bring about the gradual suppression of the abuse of opium, morphine and cocaine, as also of the drugs prepared or derived from these substances, which give rise or might give rise to similar abuses."

Among the specific obligations undertaken by the contracting powers were those of enacting effective laws or regulations for the control of the production and distribution of raw opium; of preventing the export of raw opium to countries which shall have prohibited its entry and to control the export of raw opium to countries which restrict its import; and to restrict both import and export of raw opium to that made by duly authorized persons. A less definite obligation was imposed with respect to control of prepared (smoking) opium. The contracting powers were to take measures for the gradual and effective suppression of the manufacture of, internal trade in, and use of, prepared opium, with due regard to the varying circumstances of each country concerned.

With respect to morphine, cocaine and their respective salts, the contracting powers were required to use their best endeavors to restrict import and export to authorized persons, and to enact pharmacy laws to limit exclusively to medical and legitimate purposes the manufacture, sale and use of these dangerous drugs.

The United States was one of the first countries to ratify the International Opium Convention of 1912 which eventually was ratified or acceded to by sixty-nine other countries.

FEDERAL LEGISLATION EFFECTUATING THE CONVENTION

At the time the 1912 Convention was signed the first narcotic regulatory statute of the United States, the Act approved February 9, 1909, had been in effect for over three years. This statute prohibited importation of opium and its preparations and derivatives except for medicinal purposes and absolutely prohibited the importation of smoking opium or of opium prepared for smoking. After the Convention was signed but before it was ratified, an Act approved January 17, 1914, added to the 1909 statute a prohibition against the exportation of any opium or cocaine or of any salt, derivative or preparation thereof except to a country which regulated the entry of such drugs, and in accordance with such regulations. The exportation of smoking opium or of opium prepared for smoking was absolutely prohibited. Another statute, approved on the same date, January 17, 1914, placed a prohibitive tax upon opium manufactured in the United States for smoking

purposes and placed certain other conditions upon such manufacture. These statutes implemented some of the obligations assumed by the United States under the 1912 Convention, particularly with reference to control of imports and exports.

A further important step was taken toward implementation of the obligations assumed under the 1912 Convention by the enactment of the Act of December 17, 1914, popularly known as the Harrison Narcotic Law. This statute was enacted in the form of a revenue measure and required registration and the payment of an occupational tax by all persons who produced, imported, manufactured, dispensed or otherwise dealt in opium or coca leaves or any compound, manufacture, salt, derivative or preparation thereof. All sales or transfers of these drugs were required to be made on official order forms but an exception from the order form requirement was made in favor of a registered practitioner dispensing to or prescribing for a patient in the course of professional practice only, and in favor of the registered druggist who filled the narcotic prescription. About four years later the Act was amended by adding a commodity tax stamp provision (1¢ per ounce or fraction thereof), by imposing graduated rates of occupational tax, and by certain other provisions designed to prevent evasion of these taxes. The duty of enforcing the statute was assumed by the Bureau of Internal Revenue through its field officers engaged in enforcement of all internal revenue laws. Originally, there was no separate specialized group of officers assigned exclusively to the duty of enforcing this statute.

Although enacted as an internal revenue measure, the Harrison Narcotic Law, as amended, has the effect of limiting the availability of narcotic drugs to medical and scientific uses only. It regulates production and manufacture, and distribution through channels of medical supply to the dispensing registrants, the qualified practitioner and druggist. Provision is made for use of these drugs in analytical, educational or research work by qualified scientists such as chemists and pharmacologists. Except for scientific use, the purpose of the law is to restrict ultimate consumption of these drugs to patients who have a bona fide medical need therefor, the drugs being prescribed or dispensed by a qualified practitioner in the course of his professional practice only.

The constitutionality of the Harrison Narcotic Law was challenged on two occasions in the United States Supreme Court—in 1919 and again in 1927—and in both cases the validity of the law was sustained. In 1943 the same court sustained a judgment of conviction for conspiracy against a drug manufacturer who had sold quantities of narcotic drugs to a physician, on the latter's official order forms, with knowledge of illegal sales by the physician.

Early in the history of enforcement and court-testing of the Harrison Narcotic Law as a measure controlling the domestic narcotic traffic, it became evident that there was need for a more comprehensive measure of control over imports and exports of these potentially dangerous drugs than was provided by the Act of February 9, 1909, as amended January 17, 1914. This older statute was extensively revised and in the revised form was reenacted by Congress, becoming the Narcotic Drugs Import and Export Act, approved May 26, 1922. This statute authorized the importation of such quantities only of opium and coca leaves as the then Federal Narcotics Control Board (now, the Commissioner of Narcotics) found to be necessary to provide for medical and legitimate needs. Importation of any form of narcotic drug, except such limited quantities of crude opium and coca leaves, was prohibited. Thus all derivatives of these crude drugs, such as morphine, heroin, codeine, cocaine, etc., were excluded from lawful importation, and the importation and exportation of smoking opium continued to be prohibited. Exportation of manufactured narcotic drugs and preparations was permitted under a system of control designed to assure their use for medical needs only in the country of destination. A special amendment to this statute, approved June 7, 1924, prohibited the importation of opium for the purpose of manufacturing heroin, and the legal manufacture of heroin in the United States promptly ceased.

THE GENEVA NARCOTIC CONVENTION OF 1925

In the international field, the League of Nations had assumed the function of supervising the operation of the International Opium Convention of 1912, through the Opium Advisory Committee of the Council. On January 21, 1923, a resolution was introduced in the House of Representatives of the Congress of the United States (H.J. Res. 430) requesting the President

to urge upon the governments of certain nations the immediate necessity of limiting the production of habit-forming narcotic drugs and the raw materials from which they were made to the amount actually required for strictly medicinal and scientific purposes. The resolution was approved, and an official American delegation proceeded to Geneva and presented these views to the Opium Advisory Committee in May, 1923. As a result, the Second International Opium Conference was convoked, and met at Geneva November 17, 1924, to consider the matter presented which envisaged an international agreement supplemental to or in revision of the International Opium Convention of 1912.

The American delegation to the conference was not authorized to sign any agreement which failed to recognize the necessity of controlling the production of raw opium in such a manner that there would be no surplus available for non-medical and non-scientific purposes. After more than two months of discussion the American delegation was unable to cause such a provision to be incorporated in the agreement being drafted, and withdrew from the Conference. Therefore the Convention, which was completed by the Conference on February 19, 1925, was not signed by the American delegation and the United States did not become a party to the Convention. However, the American delegation stipulated that its withdrawal from the Conference did not mean that the United States would cease its efforts through international cooperation for the suppression of the illicit traffic in opium and other dangerous drugs.

This Geneva Convention of 1925 imposed somewhat more specific obligations with respect to control of national and international trade in the drugs than were imposed by the 1912 Convention. One feature of this Convention was the establishment at Geneva of the Permanent Central Opium Board which was to "continuously watch the course of the International trade" in these drugs, collect and examine statistics, and obtain and communicate to all parties explanations of apparently excessive accumulation of the dangerous drugs in any country. The United States, although not a party to this Convention, cooperated to the fullest extent possible in giving effect to the plan of control established, and voluntarily furnished to the Board the estimates, reports and statistics that were required of a party.

THE BUREAU OF NARCOTICS

Until the year 1930 enforcement of the Federal narcotic laws had been performed by an organizational unit that was part of and subordinate to another Federal law enforcement agency. There had been, however, a growing realization of the inadequacy of such a subordinate law enforcement adjunct of another agency to cope with the important problems of control of the narcotic drug traffic, nationally and internationally. Congress therefore by an Act approved June 14, 1930, established in the Treasury Department the Bureau of Narcotics as of July 1, 1930. To this Bureau were transferred all functions and duties with respect to narcotic law enforcement formerly assigned to the subordinate unit, and the function of control of narcotic drug imports and exports theretofore performed by the Federal Narcotics Control Board, which was abolished. At the head of the new bureau, as Commissioner of Narcotics acting under the general supervision of the Secretary of the Treasury, was appointed Mr. H. J. Anslinger who had had extensive experience not only as a law enforcement administrator but also, as a former officer of the State Department, in the field of international relations.

Mr. Anslinger's major policy was to attack the supply of the illicit narcotic drug traffic at the source. He knew that smuggled drugs formed the principal source of supply of the illicit traffic in the United States: that in the case of manufactured drugs like heroin and morphine the contraband originated from excess production in Europe and the Near East, being shipped to the United States as ingeniously camouflaged cargo; and that in the case of prepared or smoking opium the contraband originated in the Far East and was carefully concealed about a vessel bound for the United States to await opportunity for clandestine landing on arrival. He developed sources of information abroad concerning prospective dispatch of such cargo, made an arrangement with appropriate law enforcement agencies in foreign countries for the informal exchange of information concerning the identity and operations of known or suspected smugglers and illicit wholesale dealers in narcotics, and secured the cooperation of the Bureau of Customs in making comprehensive searches, particularly of suspected vessels.

This action resulted in a number of seizures of large quantities of contraband narcotic drugs, including smoking opium, that might otherwise have fed the illicit traffic throughout the United States and increased drug addiction accordingly. As examples, there are mentioned the seizure at New York on December 5, 1930, after being unloaded from the S.S. Alesia from Istanbul, twenty-five cases labeled "furs," containing 17,500 ounces of contraband morphine, and the seizure aboard the S.S. President Jefferson at San Francisco September 3, 1930, of 300 five-tael tins of smoking opium (approximately 2,000 ounces) which were packed in gunny sacking and concealed in the hold under a cargo of hemp rope. These large seizures, and the arrest and conviction of those whom careful investigation could identify as responsible for the attempted smuggling, eventually resulted in discontinuance of the camouflaged cargo method as the preferred type of narcotic smuggling.

While effective steps were being taken to curb the smuggling of large quantities of contraband narcotics the new Bureau was energetically attacking the illicit domestic wholesale traffic. During the 1931 calendar year, 3,128 persons charged with violations of the internal revenue narcotic laws were convicted in the courts and total sentences imposed aggregated some 9,866 years. These cases included those of such important illicit traffickers as Richard Bayard, who sold 100 ounces of morphine for $3,500; and of Dominick Pirozzi and three associates who made three sales of 39½ ounces, 75 ounces and 100 ounces, respectively, of morphine at the rate of about $45.00 per ounce, the second sale being made at night on a dark street under protection of a machine gun held in readiness by one of the traffickers. It was necessary also to investigate and report for prosecution the comparatively few members of the professions of medicine and pharmacy found to be violating the law by prescribing or dispensing appreciable quantities of narcotics for non-medical purposes. A unique example of this type of case was that of a physician in Atlanta, Georgia, who had already been convicted on four indictments charging unlawful sales of narcotics during the period from 1921 to 1927, the latest conviction resulting in a sentence of imprisonment for two years. His license to practice medicine was revoked in October, 1929, but was restored in June, 1930. During the period slightly more than two years from June, 1930, he purchased 17 one-ounce bottles and 1,348 one-eighth ounce bottles of morphine sulphate cubes, 22,800 one-half grain morphine tablets, 1,000 one-fourth grain morphine tablets, and 218 grains of cocaine. He claimed to have dispensed narcotics to 102 "patients" in his sanitarium which proved to be a large one-story residence with several extra rooms and his office. His so-called dispensing records were obviously false. Evidence was obtained showing two sales by this physician of one dram of morphine each to a known addict in March and April, 1932, respectively, and a third sale of two drams of morphine to the same addict in July, 1932, the third sale having been made in the washroom of a clothing store. The physician was again indicted, found guilty and sentenced on October 28, 1932, to imprisonment for two years in the penitentiary. His license to practice medicine was again revoked in October, 1933, but in October, 1938, the State Board permitted him to resume practice with the proviso that he should not apply for narcotic registration for a period of twelve months. He resumed, or continued, his illegal activity with narcotics in 1941 by obtaining narcotic prescriptions from other physicians, ostensibly for his "patients," but which he caused to be filled, and sold the narcotics to addict customers. He also forged the name of another physician on a large number of narcotic prescriptions for an alleged patient, most of the morphine thus obtained being sold to others. In January, 1942, he was again indicted for violation of the narcotic law and for conspiracy (fifty-eight overt acts charged) and after conviction he was sentenced on April 14, 1942, to imprisonment for four years and one day. In October, 1942, his license to practice medicine was revoked for the third time, and an appeal for restoration of his license was refused on June 20, 1946. A few convicted physicians have been responsible for the unlawful sale or dispensing of a probably greater aggregate quantity of narcotics but none has equalled the record of sheer persistence in narcotic law violation established by this unregenerate violator.

THE CONVENTION FOR LIMITING THE MANUFACTURE AND REGULATING THE DISTRIBUTION OF NARCOTIC DRUGS OF 1931

It has already been noted that smuggled drugs formed the principal source of supply of the

illicit traffic in the United States (and in other "victim" countries) and, in the case of manufactured drugs like heroin and morphine, the contraband originated from excess production abroad. The 1912 and 1925 Conventions had enumerated general principles as to limitation of manufacture of these drugs which had not proved really effective. Therefore a conference was held at Geneva, beginning May 27, 1931, at which delegates from fifty-seven countries, including the United States, assembled to consider plans for effecting limitation of manufacture of narcotic drugs. The Commissioner of Narcotics of the United States was a member of the American delegation to this conference.

The conference drafted a momentous international agreement, briefly termed the Narcotics Manufacturing Limitation Convention of 1931, now ratified or acceded to by the United States and seventy-two other countries, which came into full operation January 1, 1934. All countries (including non-parties) were obliged to furnish annual estimates by August first of each year to the Permanent Central Board at Geneva showing their needs for each of the stated derivatives of opium and coca leaves for the ensuing year and these needs were to be based solely on medical and scientific requirements. A Supervisory Body examined these estimates and had the right to require of any country further information or details in order to make the estimate complete or to explain any statement made therein. The Supervisory Body was directed to transmit to each of the parties a statement containing the estimates for each country and, if it considered necessary, an account of any explanations given or required and any observations it might desire to make in respect of any such estimate or explanation. Thereafter each country was obligated to limit its manufacture of each of the drugs in accordance with the estimate furnished for the particular year. Statistics of actual manufacture, consumption, importation and exportation of the drugs were required to be reported periodically to the Permanent Central Board which had the right to ask any country for explanations; and if the Board found that any country was exceeding its estimate, it was required to notify that fact to all the other parties who would not, during the year in question, authorize any new exports to the offending country. The Convention also required the parties to establish (unless it was already established) a special administration for applying the provisions of the Convention; for regulating, supervising and controlling the trade in the drugs; and for organizing the campaign against drug addiction by taking all useful steps to prevent its development and to suppress the illicit traffic. In the United States this special administration was the already established Bureau of Narcotics.

This convention involved an important innovation; it was the first general international Convention which purported to create a complete system of regulations for the narcotic drug industry extending over the whole world. It contemplated the adjustment of world manufacture to legitimate world demand; the control of all channels of distribution, both national and international; it provided for narcotic drugs a system of statistical recording of all operations, both national and international; and it entrusted to international organs the task of supervising and co-ordinating the working of the whole machinery throughout the world. There can be no doubt that the effect of the operation of this Convention since it came into full effect January 1, 1934, has been to reduce drastically the production of these dangerous drugs in excess of medical and scientific needs, and therefore to reduce the supply formerly available to the smuggler and the illicit wholesale trafficker. The United States has endeavored faithfully to observe its obligations under the Convention but it is fair to state that our registered manufacturers, under the national systems of control preceding and subsequent to the Convention, had not and have not been found to be overproducing drugs that could thus be diverted to the illicit traffic.

THE MARIHUANA TAX ACT OF 1937

With continuing improvement in the control of the traffic in narcotic drugs, however, there was evidence of a growing abusive use of marihuana (flowering tops and foliage of the plant, Cannabis sativa, and their derivatives,) which was not controlled under our national laws, and the Bureau urged the enactment of a national law to control this evil. As a result the Marihuana Tax Act of 1937 was enacted, imposing the obligation of registration and payment of an occupational tax on all persons who produced, imported, manufactured, sold or transferred this substance. An important feature of this law was the imposition of a heavy transfer tax, at the rate of $100 an ounce, on all sales or transfers

of marihuana to an unregistered person, with heavy penalties imposed for non-compliance on either transferor or transferee. After the statute was enacted the Commissioner of Narcotics obtained the cooperation of a number of State, county and municipal authorities and continues to seek cooperation of all such government agencies to locate and destroy all wild or volunteer growth of the cannabis plant within their respective areas.

THE CONTRABAND SEIZURE ACT

The smuggler and the peddler of contraband narcotics and marihuana frequently uses an automobile as a facility for transfer and concealment of his illicit wares; it not only expedited deliveries to his customers but provided a better opportunity for a quick get-away afterward. Under an Act of Congress approved August 9, 1939, any vessel, vehicle or aircraft used to facilitate the transportation, sale, concealment, possession, etc., of contraband narcotics or marihuana becomes forfeited to the government and may be seized, for forfeiture, by the enforcement officer. Many such vehicles have been seized by agents of the Bureau of Narcotics and, being forfeited to the government, provision is made for the retention by the Bureau of such number of these vehicles as may be necessary for official use in enforcement work. The statute has proved to be effective in converting a facility for law violation when in possession of the smuggler or peddler into a facility for law enforcement in possession of the law enforcement agent.

THE OPIUM POPPY CONTROL ACT OF 1942

Due to the shortage of supplies of imported poppy seed after the beginning of World War II certain persons in the United States started to grow the opium poppy, ostensibly for seed yield, ignoring friendly warnings communicated by the Commissioner of Narcotics that the seed pods contained morphine which could and would be readily extracted, even in impure form, by peddlers with the inevitable result of spreading drug addiction. The Commissioner sought and obtained the enactment of special legislation—the Opium Poppy Control Act of 1942—which prohibited the growth of the opium poppy in the United States except under a special license issuable only upon a demonstrated need for domestic production of the opium poppy to supply opium derivatives for medical and scientific uses. No such need has arisen nor is it likely under modern developments that such need will ever arise, and no licenses have been issued. The few crops of opium poppies that were growing were seized and destroyed.

THE PROTOCOL OF 1946

The supervision of operation of the several narcotic Conventions had been performed by an Opium Advisory Committee of the Council of the League of Nations which went out of existence upon the organization of the United Nations. There was now organized the Commission on Narcotic Drugs of the Economic and Social Council of the United Nations, and Mr. Anslinger was appointed the United States representative on this Committee. He proposed an agreement which was adopted as the Protocol of 1946 whereby all functions assigned under the several conventions to organs of the now defunct League of Nations were transferred to corresponding organs of the United Nations. Thus the new Commission on Narcotic Drugs assumed the functions of the old Opium Advisory Committee.

SYNTHETIC NARCOTIC DRUGS

Demerol® was the first drug produced synthetically and recommended for analgesic use as a substitute for the pain-relieving opium derivatives and bearing no direct chemical relationship to morphine. When the result of tests by the U. S. Public Health Service indicated that the new drug possessed addiction-liability similar to morphine, the Bureau sought and obtained enactment of a special statute, approved July 1, 1944, making the Federal narcotic laws applicable to the new drug under the statutory designation "Isonipecaine." However, it became known that other new synthetic drugs being developed had comparable analgesic properties and might be found to possess addiction-liability. The Bureau sought and obtained the enactment of a statute, approved March 8, 1946, which established a general procedure for the expeditious application of control measures to any drug found to be dangerous from the addiction-liability standpoint. Under this statute the Federal narcotic laws are made applicable to any drug found by the Secretary of the Treasury, after due notice and opportunity for public hearing, to have addiction-liability similar to morphine

or cocaine, and proclaimed by the President to have been so found by the Secretary. The Secretary, in making such findings, and the Bureau of Narcotics in determining general questions of policy where chemistry and pharmacology of narcotics or marihuana are involved, receive invaluable cooperation by way of scientific research and advice, and technical service from the United States Public Health Service and the Committee on Drug Addiction and Narcotics of the National Research Council. Eleven new synthetic analgesic drugs have been made subject to narcotic control by this procedure but only a few of these drugs have been made available for general medical use, examples being methadon® (dolophine® or adanon®), nisentil® and dromoran.®

Meanwhile Mr. Anslinger had proposed an international agreement, in the nature of an addition to the 1931 Convention, which was adopted and became effective as the Protocol of 1948. This Protocol establishes international procedure, analogous in principle to that established in the United States by the Act of March 8, 1946, whereby new drugs found to have dangerous addiction-liability are promptly brought under control imposed by the 1931 Convention, the definitive finding in this case being made by the World Health Organization. Up to the present time the findings of the Secretary of the Treasury under the national law and the findings of the World Health Organization under the 1948 Protocol, with respect to addiction-liability of the same new drugs, have been in accord.

RECENT NATIONAL ACTION

Addiction among teen-agers was highlighted during 1950 and 1951 by much newspaper publicity. There is no doubt that there was somewhat of an increase in drug addiction, a phenomenon associated with unsettled social conditions following the late world conflict, observable in other countries as well as the United States. Teen-age addiction in the United States was largely confined to metropolitan centers; most of these addicts were of the delinquent or near-delinquent type who were not attending school; and many of them had criminal records before they came to the attention of authorities as drug addicts.

It was ascertained that heroin, probably the most potent and therefore the favorite narcotic drug of addiction, was being smuggled into the United States from Italy and Turkey, and probably indirectly from China and Greece. The Italian authorities, as a result of successive disclosures of large-scale diversion of heroin from local factories and wholesale drug houses, reduced heroin estimates from 190 kilos to 50 kilos, and later to 30 kilos; there were stocks on hand, however, of 200 kilos, equal to about a ten-year supply. Upon urgent representations by Mr. Anslinger through the United Nations Commission on Narcotic Drugs, the Italian authorities agreed to permit no further manufacture of heroin for ten years or until the existing stock was exhausted. The Turkish delegate to the Commission announced that his government had placed control restrictions on the importation of acetic anhydride used in the manufacture of heroin; this would have effect in curbing production of heroin by clandestine factories supplying the smugglers; and the hope was expressed that the Turkish government would place more severe restrictions on the internal distribution of opium. Request was made that the Secretary-General send a communication to the Greek government asking for increased vigilance with respect to supervising the heroin traffic. In view of the reported flow of heroin from Tientsin and points in Manchuria into Japan via Hong Kong, some of which was finding its way into the United States and other countries, substantiated by two large seizures in Japan of forty and twenty pounds, respectively, of heroin which undoubtedly originated in Tientsin, North China and Manchuria, the Commissioner of Narcotics urged upon the Commission that this traffic should be suppressed by the Communist authorities in China.

National law enforcement continued with even greater vigor, and during the year 1951 a large number of the leading wholesale illicit distributors with their cohorts were convicted and sentenced, including such notorious violators as Waxey Gordon, Harold Meltzer, Abe Chapman, Max Kornhauser, Anthony Granza, Eugene Tramaglino and Joseph Orsini. The Bureau recommended the enactment of the Boggs bill which became the Act of Congress approved November 2, 1951, imposing minimum sentences of two, five and ten years, respectively, for a first, second, and third or subsequent offense of violating the narcotic or marihuana laws. There is already evidence of the deterrent effect of this statute, especially with respect to

peddlers who have a record of one or more violations of these laws and who fear the practical certainty of the heavier recidivist penalty if again convicted. Congress made available to the Bureau an increased appropriation permitting added facilities whereby the agency is even more comprehensively investigating, detecting and eliminating the major sources of illicit supply of narcotic drugs and marihuana.

These activities have extensively curbed the illicit traffic in the United States through drastic reduction in contraband supplies available to it and the elimination of many of its channels of distribution.

By Executive Order 10302, issued November 2, 1951, the President established the Interdepartmental Committee on Narcotics composed of representatives of the Departments of the Treasury, State, Defense, Justice, Agriculture, and the Federal Security Agency, the Commissioner of Narcotics having been appointed Chairman of this Committee. One of the duties of the Committee is to examine and study problems and developments arising in the administration and enforcement, national and international, of the laws and conventions relating to narcotic drugs and marihuana. This Committee may advise on problems arising in connection with the enforcement of the narcotic and marihuana laws but it does not formulate or direct enforcement policy which remains the primary responsibility of the Bureau of Narcotics.

RECENT INTERNATIONAL ACTION

We have seen that the American delegation to the Geneva Conference of 1925 was not successful in having incorporated in the Convention of 1925, then being drafted, a provision that would be effective in limiting the production of crude opium and coca leaves (through restriction of the growth of the opium poppy and the coca bush) to that required for the world's medical and scientific needs. In the session of the United Nations Commission on Narcotic Drugs, Mr. Anslinger as the American delegate proposed and continued to urge the necessity of an international agreement so limiting the production of the crude drugs. As a result the Commission is developing a protocol for limiting the production of opium and the principles on which the protocol may be based have been agreed upon.

Another important project before the Commission is the drafting of a Single Convention which will consolidate, with suitable revision in the light of experience, the various narcotic conventions and protocols into a single international agreement. The American delegate is taking a very active part in this difficult task of formulating what will actually be a code of international legislation on control of narcotic drugs, including the synthetic substitutes and marihuana. It will be noted that the barbiturates and other somnifacient drugs are not included in the present system of international control, nor are they subject to the narcotic laws of the United States; it would appear obvious that these drugs which are not subject to international control should not be brought within the purview of the national narcotic laws in view of the closely coordinated and interrelative international and national system of control applicable only to narcotic drugs and marihuana. While it is recognized that the barbiturates are subject to a degree of abusive use within the United States, there are rather different aspects to the problem of their control of a nature and scope different from and independent of the legislation controlling narcotic drugs and marihuana.

Reviews

A Psychomedical Survey of a Private Outpatient Clinic in a University Hospital*

BERNARD I. LEWIS, M.D.†

Iowa City, Iowa

THERE has been much recent comment on the importance of emotional factors in everyday medical practice. The claim has been made[1–4] that one-third to two-thirds of all patients are suffering predominantly from psychic disorders with minimal if any structural disease. Robinson's studies[5,6] on a large group of indigent patients from the medical clinics of the Johns Hopkins Hospital tend to confirm these statements. Roberts and Norton[7] obtained similar findings in a low income group of patients investigated in the medical outclinic of the New Haven Hospital. Allan and Kaufman[8] reported a lower but still striking incidence in their series of patients from the Lahey Clinic. To provide further information on the prevalence and role of such disorders in the ambulatory patient population, the present study of a patient group from the Private Outpatient Service (POPS) of the Johns Hopkins Hospital was undertaken. In contrast with Robinson's indigent cases and Roberts and Norton's low income group, our patients were all private patients and stemmed from different socioeconomic levels. They possibly differed medically from the Lahey patients, too, as that clinic is noted particularly for its surgical experience. The structure and function of the POPS has been described in detail by Futcher;[9] hence, it will suffice to mention here that it is a general diagnostic medical clinic which is neither noted for nor emphasizes any particular specialty. On arrival, patients are assigned without selection to one of several Fellows who directly conducts the investigation. This is carried out in close collaboration with a senior medical consultant who also has been routinely assigned to the case. In addition the opinion of special consultants in other fields is very frequently obtained. Thus these patients are studied by two or more physicians and the final diagnoses are based on several carefully considered opinions. The investigation usually encompasses a period of five days during which time the patient is interviewed at least twice and, when indicated, more frequently. A detailed report of the complete investigation, including the final diagnoses and therapeutic recommendations, is subsequently forwarded to the home physician to whom the patient is routinely returned.

The data from 163 such patients, successively and routinely assigned to the writer in his capacity as the Fellow directly conducting the medical investigation, provide the material for this report. With rare exception, all patients were interviewed in the same fashion so that, regardless of the apparent nature of the illness, an attempt was made to review the life history and the pertinent psychosocial information. As a result of his previous experience with the emotional aspects of medical problems the writer was able to extract most of this material during the routine work-up. On occasion, however, this was supplemented by data from the psychiatric consultant's report. The general characteristics of the total patient group will first be presented to outline broadly the type of patient attending this clinic. Then, to clarify

* Based on studies performed during the tenure of a Fellowship in the Department of Medicine, Johns Hopkins University School of Medicine, and the Private Outpatient Service, Johns Hopkins Hospital.

† Assistant Professor of Medicine and Director, Psychosomatic Program, Department of Internal Medicine, College of Medicine, State University of Iowa.

the medical characteristics and emotional problems, detailed analysis and comparison of various subgroups will be made.

GENERAL CHARACTERISTICS OF THE TOTAL PATIENT POPULATION (TABLE I)

The 163 patients were fairly evenly divided by sex. Ninety-five per cent were white and 90 per cent were residents of North America with the majority residing outside the state of Maryland. The majority were middle-aged with but 6 per cent under the age of thirty. Their educational and occupational backgrounds were distinctly superior to those of the general population as revealed by recent Bureau of the Census data.[10] More than one-third of the patients had attended a university, three times the incidence in the population at large, and approximately twice as many of the patients fell into professional and white collar groups. Analysis of the marital status disclosed another striking disparity between our patients and the total population. Sixteen per cent of the patients had been divorced as contrasted with only 2.2 per cent for all persons in the United States over the age of twenty-five.

TABLE I

GENERAL CHARACTERISTICS OF TOTAL PATIENT POPULATION

No. of patients	163	
Sex: Men	78	
Women	85	
Color: White	95%	
Residence: North America	90%	
Age: Mean	48 years	
Decade spread: 3rd	6%	U. S. Total Population over 25 (1950 Census)
4th–6th	78%	
7th	16%	
Marital Status: Single	9%	9.8%
Married	66%	74.6%
Divorced	16%	2.2%
Widowed	7%	13.4%
		U. S. Total Population (1947 Census)
Education: Public School	19%	49.5%
High School	39%	36.8%
University	37%	12.1%
Unknown	5%	
		U. S. Total Male Population (1950 Census)
Occupation (Men only):		
Professional	20%	8.9%
White Collar	65%	37.8%
Skilled Labor	9%	41.5%
Miscellaneous	6%	11.8%

In summary, our "mean" patient was a white North American in his (or her) late forties, probably married, and distinguished from his (or her) counterpart in the general population by superior educational, economic and occupational achievements but seven times more likely to have been divorced.

GROUP BREAKDOWN

The patients have been grouped, as below outlined, to permit closer study of their background, medical and otherwise, the features of their current illness and, in particular, the role of psychic factors.

Group I. Thirty-nine patients, 24 per cent of the total patient population, with demonstrable organic disease but without detectable "psychopathy."

Group II. Eighty-one patients, 49 per cent of the total patient population, with demonstrable psychogenic disorders but without detectable organic disease.

Group III. Six patients, 4 per cent of the total patient population, with both psychic and somatic components in their illness who were basically stable individuals.

Group IV. Thirty-seven patients, 23 per cent of the total patient population, with both psychic and somatic components in their illness who were basically unstable individuals.

The terms "psychopathy" and "psychogenic disorder" are used synonymously in this paper to denote significant alterations in affect, behavior and/or physiologic function arising from psychologic forces. These mechanisms were adjudged entirely responsible for the present illnesses of the group II patients whereas in groups III and IV they were regarded as operating in conjunction with various structural lesions to produce the current symptoms and signs. The terms "organic disease" and "somatic component" refer to structural lesions of organic pathogenesis which were of sufficient significance to have disturbed the patient and prompted him to seek medical aid.

These psychogenic diagnoses were achieved on a positive basis. They did not rest simply upon the exclusion of organic pathologic processes, nor did they rely upon evidences of past neurotic behavior. The positive diagnostic criteria were germane to the present illness and, in brief, required (1) that the current symptoms and signs should be characterized by an onset,

sequence, manifestations and course which strongly suggested disturbed psychophysiologic function; (2) that thorough physical and laboratory examinations should disclose either no pertinent structural lesions or, in the group III and IV illnesses, organic disease which explained only partially the total picture; (3) that there should be delineated some stressful life situation (or internal conflict) which currently was providing the patient with significant difficulties; (4) that the patient's response to this stress should be correlated, in significance, with the current symptoms and signs, that is, that these manifestations reflected, psychophysiologically, the unresolved dilemma or a partial but unsatisfactory solution to the problem; and (5) that the impact of this stress should be correlated in time with the onset, exacerbation and/or perpetuation of the present illness.

The evaluation of basic emotional stability or instability (groups III and IV), although based similarly on positive criteria, was not so much concerned with the features of the present illness as with evidences of past neurotic behavior. The differentiation rested upon (1) the calibre of the patient's over-all life adjustments as exemplified in the economic, social and marital analyses to be presented and (2) the past medical and psychic characteristics with particular reference to the presence or absence of recurring patterns of psychophysiologic dysfunction, especially when evoked by relatively minor and ordinary stresses.

The four sections to follow are devoted to the analysis and intergroup comparison of various background characteristics antecedent to the current illness. For this reason it was deemed valid to combine "stable" group III with I and "unstable" group IV with II, thus providing two larger groups of greater homogeneity for statistical purposes. These will be referred to hereafter as A (groups I and III) and B (groups II and IV).

Although to be discussed in further detail, it is even now obvious, from the primary breakdown, that psychic and psychophysiologic factors had assumed significance in the current illnesses of 76 per cent of the total patient population (i.e., the sum of groups II, III and IV).

GENERAL AND SOCIO-ECONOMIC CHARACTERISTICS, BY GROUP

Table II reveals that group A contained approximately one-fourth of the patients, in a ratio of three men to one woman, with a mean age of fifty-two. The educational attainments of both groups were almost identical. The A patients presented stable occupational histories with infrequent job changes and little dissatisfaction with their current employment, co-workers or employer. Only 4 per cent admitted to any financial difficulties.

TABLE II
GROUP CHARACTERISTICS: GENERAL AND SOCIO-ECONOMIC FEATURES

	Groups	
	A Stable	B Unstable
No. of patients	45	118
% Total population	28	72
Sex: Men	33	52
Women	12	66
Mean Age	52	46
Job instability %	0	14
Job dissatisfaction %	7	35
Financial worries %	4	20
"Dys-sociability"* %	9	30
"Sub-interests"† %	7	44

* Deviations and difficulties in social relationships
† Restricted range of off-work interests and activities

In contrast, group B comprised almost three-fourths of the patient population, with a predominance of women and a mean age of forty-six. Fourteen per cent had unstable work records and 35 per cent had current job difficulties. Twenty per cent were seriously concerned with financial problems.

Satisfying social relationships and, according to Ruesch,[11] specialized off-work activities provide valuable outlets in times of stress and enhance the ability to tolerate frustration. They tend to be characteristic also of a well integrated personality. Thus individuals who are inordinately seclusive or excessively gregarious, and those having grossly curtailed or never developed off-work interests and hobbies may be predisposed to or actually struggling with emotionally engendered problems. Accordingly our patients were examined for significant deviations of this nature in their backgrounds. As outlined in Table II, 9% in group A evidenced dysfunction in sociability ("dys-sociability") while 7 per cent revealed a restricted range of interests and activities ("sub-interests"). By comparison, 30

per cent of group B had such social difficulties and 44 per cent had few or no specialized interests over and above their daily work. The group B sex ratios here revealed a feminine predominance of 3:1 and 2:1, respectively.

These findings are compatible with the concept that unstable persons have a generalized maladjustment that is reflected in many spheres of activity.

MARITAL CHARACTERISTICS, BY GROUP

Marriage is a singularly important step and frequently a severe testing ground of emotional maturation and stability. Many never marry, or are divorced, because of psychic difficulties. Others marry unusually early or unduly late in life for similar reasons.

It was thus of interest, as detailed in Table III, that approximately three times as many group B patients had never married or had been divorced, as was the case in group A. Here again the sex ratio in group B revealed a 2:1 preponderance of women. This incidence of divorce takes on added significance when compared with the current Bureau of Census figures for the general population over the age of twenty-five (see Table I) and is quite similar to Ruesch's findings[11] in patients with psychologic invalidism.

Marriage at an early age is frequently utilized as an escape mechanism from an unhappy home environment, especially by women. Conversely, and applying particularly to men, marriage late in life is often associated with excessive parental dependence, usually upon the mother. Of our patients, 4 per cent in group A married prior to the age of twenty as compared with 14 per cent in group B. The sex incidence here was almost completely feminine, the ratio being 16:1. There was no intergroup disparity in regard to late marriages (Table III) but the men predominated in a ratio of 3:1.

The duration of the first or only marriage is similarly of interest. Divorces occurring early may suggest emotional immaturity whereas, when occurring later, may indicate a straying of masculine attention and affection. No group A patient had been divorced within the first year and only 4 per cent within the first five years of their marriage. In group B, however, 4 per cent were divorced within the first year and 13 per cent within the first five years.

The analysis for significant current marital discord revealed an incidence of 7 per cent in group A as contrasted with 45 per cent in group B. Sexual maladjustment, such as acquired impotence (libido and potentia previously present and satisfactory) and frigidity, frequently arises from psychic difficulties. The incidence was 9 per cent for group A but 29 per cent for group B. Enhancing this disparity is the fact that half of these group A individuals (all men) were suffering from portal cirrhosis which may have been contributory. There were no such associated organic factors in the group B patients where the sex ratio was 1:1.

TABLE III
GROUP CHARACTERISTICS: MARITAL FEATURES

	Groups		Unstable Group Ratio M:W
	A Stable (%)	B Unstable (%)	
Never married	4	11	1:2
Divorced	7	19	3:4
Age first marriage:			
Under 20	4	14	1:16
Over 30	13	14	3:1
Duration first marriage:			
Less than 1 year	0	4	....
Less than 5 years	4	13	1:6
Marital discord	7	45	....
Sexual maladjustment	9	29	1:1
Children per marriage:			
Childless	27	46	....
Four or more	20	5	....

It is said that children bind the family ties more closely. Certainly the procreative instinct is one of our basic drives. Discord is believed to be more prevalent in childless marriages and the reverse to prevail in homes with multiple offspring. In line with these concepts 46 per cent of the married patients in group B were childless while only 5 per cent had four or more children. These figures gain added significance when compared with those of group A. (Table III.)

In summary, emotionally unstable individuals, while predisposed to psychogenic illnesses, seem overly susceptible as well to "ailments" in the marital sphere. This is reflected in group B by the incidence of unmarried adults, of unusually early, short-lived and childless marriages, of sexual maladjustment and marital discord in general.

PAST MEDICAL CHARACTERISTICS, BY GROUP

The frequency with which an individual seeks medical advice correlates closely with the status of his health. This is true particularly of psychogenic illnesses which are characterized usually by their chronicity, although often punctuated by acute exacerbations, and the persistence of these patients in their fruitless quest of a "magic" drug or operation.

TABLE IV
GROUP CHARACTERISTICS: PAST MEDICAL FEATURES

	Groups		Unstable Group Ratio M:W
	A Stable (%)	B Unstable (%)	
Medical "shoppers"	4	14	1:2
Chronic and/or recurring ill health	4	36	1:2
Hospitalizations:			
None	27	8	...
Four or more	4	27	2:3
Surgery:			
None	36	8	2:1
Three or more	9	29	1:3
Gynecologic surgery	17	56	...
Cholecystectomy / Gastrointestinal laparotomy	4	13	...
"Psychomedical habits"*	22	59	...

* Excessive indulgence in alcohol, barbiturates, tobacco and laxatives

Table IV contrasts the medical and surgical features of groups A and B and reveals the higher incidence in the latter of medical "shoppers," chronic and recurring ill health, hospitalization and surgery. Of particular interest, 27 per cent of group A had never been hospitalized and 36 per cent had never undergone surgery (requiring a general anesthetic) while such applied to only 8 per cent of the patients in group B. The sex ratio in these group B indices showed a preponderance of women varying between 2:1 and 3:1. The prevalence of gynecologic surgery indicated an even greater intergroup disparity with such procedures having been performed in 56 per cent of the B group women in comparison with 17 per cent of group A. Previous studies[11,12] have stressed the unfortunate frequency of pelvic operations in emotionally disturbed women, performed so often without either sound preoperative indication or postoperative benefit. Similarly, cholecystectomy and gastrointestinal explorations are often performed for ill-defined abdominal complaints basically psychogenic in origin. Although the incidence of such procedures was not unusually high, still the group B prevalence was approximately three times that of group A.

There are certain "habits," fairly common in our society, which attain psychomedical significance when carried to excess. Overindulgence in alcohol, tobacco, laxatives and barbiturates is representative of such unhealthy patterns and their incidence and severity closely parallel the emotional tension and instability of the individuals concerned.[11] Analysis in this regard disclosed a total percentage of 22 in group A as contrasted with 59 per cent in group B.

Thus in keeping with the social, economic and marital findings, the relationship of emotional factors is again reflected in the past medical and surgical records.

PAST PSYCHIC CHARACTERISTICS, BY GROUP

Stressful life situations are particularly traumatic for the child. (Table v.) It is believed by many that the imprint of early psychic stress is probably never erased and bears importantly on the production of emotional illness in later life, even though the interplay of many other factors is involved.[13] Especially disturbing to the child is a home environment characterized by alcoholism, brutality, poverty, parental rejection or shattered by the early death or divorce of the parents. These and other striking features of a stressful childhood were extracted, as shown in Table v, from the past histories of 33 per cent of the group B patients as compared with 4 per cent in group A. Strongly suggestive findings were obtained in another 19 per cent in group B and 7 per cent in group A. Thus over one-half of the group B patients had been subjected in varying degree to significant emotional trauma in childhood. The sex ratio again indicated a 2:1 preponderance of women.

It is stated[11] that the youngest and eldest siblings or only child tend most frequently to develop psychic problems. The youngest sibling is commonly the "baby" of the family and thus predisposed toward emotional immaturity. The eldest, conversely, is often burdened prematurely by more responsibility than he can shoulder. The only child is usually overprotected, which fosters both dependency and egocentricity. Although 54 per cent of the group

B patients fell into one or another of these categories, the only striking intergroup difference pertained to the incidence of youngest siblings.

The temporal correlation of traumatic events with the onset of psychogenic disorders is of great significance. However, the etiologic validity

TABLE V
GROUP CHARACTERISTICS: PAST PSYCHIC FEATURES

	Groups		Unstable Group Ratio M:W
	A Stable (%)	B Unstable (%)	
Stressful childhood environment:			
Striking	4	33	1:2
Suggestive	7	19	1:2
Sibling status:			
Youngest	7	21	1:2
Oldest	27	28	1:2
Only child	6	6	1:1
"Psychopathy"*			
Acquired familial patterns:			
Striking	0	21	1:2
Suggestive	0	4	2:3
With childhood stress:			
Striking	2	27	1:2
Suggestive	0	9	1:2
With adult stress	7	46	1:2
With pregnancy	0	17	...
With menopause	0	19	...
With illness	2	34	1:2
With surgery	0	27	1:5
With weight variations	0	25	1:4
Prior psychiatric treatment	0	7	1:3

* Psychogenic disorders

of such circumstantial evidence cannot be tacitly assumed for each of us is confronted with adversity and misfortune at various times in our journey through life. Much more significant is the manner in which we respond to stress, with the degree and pattern of our responsivity bearing importantly on the production of illness and disease and providing a measure of our emotional stability. Many of our basic response patterns are "learned" during infancy and early childhood and, becoming ingrained, tend to repeat themselves throughout life. Thus there may develop a "conditioned" psychic and psychophysiologic over-responsivity which, according to Wolff,[14] plays an important role in the determination of the organs or body systsem most prominently affected by so-called psychosomatic diseases in later life. Children are especially prone to acquire such response patterns from members of their family group, particularly the parents.[15] The organ systems most commonly involved in these mechanisms are the gastrointestinal, cardiovascular and musculoskeletal. In Table v it will be seen that, while absent in group A, various acquired familial patterns of unhealthy responsivity were detected in 21 per cent of group B with suggestive evidence in another 4 per cent. Furthermore, although a familial relationship could not be clearly demonstrated, excessive psychophysiologic responses to stress during childhood had occurred in 27 per cent of group B, with suggestive findings in another 9 per cent, but were detected in only 2 per cent of group A. Similar manifestations during adult life had occurred in 46 per cent of the group B patients in contrast with 7 per cent in group A. The sex breakdown, as previously, demonstrated a 2:1 predominance of women.

The incidence of these unhealthy patterns of response to the impact of such common stresses as pregnancy, the menopause, medical illness and surgery was specifically analyzed. In group A, aside from a 2 per cent prevalence in conjunction with an illness, the findings were otherwise negative. By comparison (Table v), an incidence of from 17 per cent to 34 per cent was found in the group B patients, again with a striking feminine preponderance.

Another response pattern commonly manifested during disturbing life situations pertains to disorders of appetite and food intake. These dietary alterations may be quite severe and result in gross obesity at the one extreme to striking malnutrition of the anorexia nervosa type at the other.[16] The frequency with which weight variations developed in a setting of situational stress and emotional upset was therefore determined. In concurrence with the other unhealthy response patterns there was revealed a zero incidence in group A but 25 per cent in group B. The sex ratio here was 4 women to 1 man.

No member of group A had ever sought or been referred for psychiatric consultation. It is curious that, in spite of these many background features of instability, only 7 per cent of group B had received psychiatric attention. It is true that many may have refused to accept such advice but, as the data later suggest, it is likely

that medical lack of recognition and misdiagnosis may be held equally culpable.

Summarizing then, the group B patients revealed a high incidence of early environmental stress with disruption of the family constellation especially prominent. Over half had occupied one of the more vulnerable sibling positions and there was a high prevalence of unhealthy psychophysiologic over-responsivity to the vicissitudes of life. No group A patient and only a few in group B had ever consulted with a psychiatrist in the past.

CHARACTERISTICS OF THE PRESENT ILLNESS, BY GROUP

For analysis of various features of the present illness our patient population has been regrouped on the basis of the presence or absence of psychogenic factors in the current medical picture. In actuality this necessitated merely a transfer of the small number (4 per cent) of stable "mixed" cases (primary group III) from group A. Thus two groups still remain, one composed of patients with organic disease alone (henceforth group O) and the other comprising those with significant psychic components in their illness (henceforth group P). Group O contains thirty-nine patients and group P 124 patients, 24 per cent and 76 per cent, respectively, of the total patient population. Tables VI and VII present certain subjective and objective data on their current medical problems.

As noted in Table VI, 41 per cent of the group O patients had requested their own appointment, while group P had almost twice this incidence. This is consistent with the medical "shopping" tendencies, the incessant search for the "magic cure" and the recurring dissatisfaction of the group P individuals with their medical attendants when such relief was not quickly forthcoming.

The details of the current illness and their mode of presentation usually yield significant information on the role of psychic factors.[17,18] Such was the case in 62 per cent of group P whose historical efforts and chief complaints were so vague, irrelevant, dramatic and/or bizarre as to arouse immediate suspicion that this was not a straightforward "organic" process. Only 18 per cent in group O demonstrated such characteristics.

The areas involved by the chief complaints are fairly similar in both patient groups. Table VI reveals that approximately 60 per cent of each group primarily implicated one or another of four systems—the gastrointestinal, cardiovascular, musculoskeletal and genitourinary. Although group O had a higher incidence of musculoskeletal complaints, there were no quantitative intergroup differences of consequence. The distinguishing feature was the vague, irrelevant and often bizarre character of these complaints in group P. A singular disparity was the 18 per cent incidence of ill-defined and/or peculiar pain or nervousness in group P without a single such instance in group O. Alvarez[16] has commented in detail on the frequency and significance of such complaints in his patients with emotionally dictated problems.

TABLE VI
CHARACTERISTICS OF PRESENT ILLNESS: SUBJECTIVE

	Group O* (%)	Group P† (%)	Group P† Ratio M:W
% Total population	24	76	4:5
Self-appointment	41	73	2:3
Non-specific, bizarre complaints	18	62	2:3
Chief complaints:			
Pain	0	11	1:3
Nervousness	0	7	1:3
Gastrointestinal tract	21	25	1:2
Cardiovascular system	8	13	1:2
Musculoskeletal system	25	14	1:1
Genitourinary tract	8	7	All W.
Multiple chief complaints	3	75	.. ..
Acute onset	21	18	.. ..
Duration:			
1 year or less	41	31	2:1
5 years or more	21	34	2:3

* Those patients with organic disease alone
† Those patients with significant psychogenic disorders

In contrast to 3 per cent in group O, 75 per cent of the group P patients had multiple (three or more) chief complaints, which is so typical of emotionally disturbed individuals. The onset of the present illness was gradual and often insidious in nearly 80 per cent of both patient groups indicating that patients with acute processes do not commonly attend this clinic. Consistent with this the duration of the present illness was one year or less in approximately one-third of the patients, 41 per cent in group O and 31 per cent in group P. The remainder had protracted illnesses, with 34 per cent in group P and 21 per cent in group O having their current

complaints for five years or more. The significance of the intergroup disparities here, suggesting rather shorter illnesses in group O, is questionable.

The appearance and behavior of many of the patients was most striking. As indicated in Table VII, 77 per cent in group P displayed objective evidence of affective and psychophysiologic dysfunction grossly out of proportion to any structural disease that might have been present. Another 10 per cent in group P appeared superficially and inappropriately "calm" despite considerable underlying emotional turbulence. The writer has been impressed in the past with this inappropriately "calm" demeanor which, at times, is quite misleading. This benign facade is particularly characteristic of certain patients with ulcerative colitis and essential hypertension. The facies tends to be bland, smooth and unwrinkled, with an almost beatific quality in the colitis cases whereas in the hypertensives there is evident a tinge of thinly disguised tension.

TABLE VII
CHARACTERISTICS OF PRESENT ILLNESS: OBJECTIVE

	Group O* (%)	Group P† (%)	Group P† Ratio M:W
Appearance:			
"Disturbed"‡	0	77	1:1
"Calm"§	0	10	1:1
Salient signs:			
Structural only	100	0	...
Structural and psychophysiologic	0	34	2:1
Psychophysiologic	0	66	1:2
Gag reflex:			
Hyperactive	2	15	2:1
Hypoactive or absent	15	35	2:3
Deep tendon reflexes:			
Hyperactive	23	44	2:3

* Those patients with organic disease alone
† Those patients with significant psychogenic disorders
‡ Objective evidence of excessive psychic distress
§ Inappropriate superficial calmness belied by underlying tension

The analysis of the salient signs in Table VII reveals that structural changes commensurate with the symptoms were present in all group O patients. By contrast, 66 per cent of group P revealed only affective and/or psychophysiologic disturbances while in 34 per cent such emotionally conditioned reactions co-existed with various organic lesions. The organic processes in several of these "mixed" patients, however, were unrelated to the current complaints, minimal in degree and often asymptomatic.

Many indications of psychophysiologic dysfunction were noted during the physical examinations but have not been analyzed. These included manifestations of peripheral autonomic imbalance, such as hyperhidrosis, dermographism, pupillary alterations, tremors, muscular spasms, sighing respiration, hyperventilation, rhinorrhea, sialorrhea and undue lability of the heart rate and blood pressure. Two objective test responses, the deep tendon and gag reflexes, have been analyzed, however, and are recorded in Table VII. Alterations of the deep tendon reflexes, usually in the direction of hyperactivity, have been commonly detected in emotionally disturbed individuals.[21] Such hyperactive responses were present, without organic basis, in 23 per cent of group O as compared with 44 per cent of group P patients. The responsivity of the gag reflex appears to be affected by psychic factors also but more commonly in the opposite direction. Thirty-five per cent of the patients in group P had an hypoactive to absent gag reflex while in 15 per cent there was an hyperactive response. The comparable group O figures were 15 per cent and 2 per cent. Such physiologic aberrations are easily detected and, when properly evaluated, contribute importantly toward substantiation of a correct diagnosis.[20]

There are many symptom-complexes currently believed to stem from or be contributed to importantly by psychophysiologic mechanisms. Two hundred twenty-seven such syndromes were detected in ninety-six of the group P patients. Of these 185 fell into one or another of three main systems—the gastrointestinal, cardiovascular and musculoskeletal. These data are presented in Table VIII. In all cases positive evidence was at hand to confirm the psychogenic role while, conversely, no organic basis could be elicited.

There were ninety-eight gastrointestinal disorders, the majority of which involved the large bowel and fell into the so-called irritable colon syndrome.[22] On the basis of recent studies[23] these have been subdivided into spastic constipation and functional diarrhea. Twenty-three patients had dyspeptic complaints suggestive of peptic ulcer but in only three was positive x-ray evidence obtained. These three patients are

included in group P on the basis of the positive diagnostic criteria previously outlined, not merely because they had peptic ulcers. Another nineteen patients referred their problems to the upper gastrointestinal tract as well but here, aside from features suspicious of recurring cardio

TABLE VIII
CHARACTERISTICS OF THE PRESENT ILLNESS: PSYCHOPHYSIOLOGIC SYNDROMES—GROUP P* PATIENTS

System	Incidence		
	Total	Men	Women
Gastrointestinal: Total	(98)	(33)	(65)
Sialorrhea	2	1	1
Irritable upper gastrointestinal tract	19	2	17
Irritable lower gastrointestinal tract			
(a) Spastic constipation	46	16	30
(b) Functional diarrhea	8	2	6
Ulcer syndrome			
(a) Positive x-ray	3	3	0
(b) Negative x-ray	20	9	11
Cardiovascular: Total	(41)	(14)	(27)
Neurocirculatory asthenia	17	9	8
Neurogenic hypertension	12	3	9
Vasodepressor syncope	7	2	5
Periodic headache	5	0	5
Musculoskeletal: Total	(46)	(14)	(32)
Tension headache	30	8	22
Myalgia			
(a) Cervical	5	3	2
(b) Lumbar	4	2	2
Polyarthralgia	7	1	6
Grand Total	(185)	(61)	(124)

* Those patients with significant psychogenic disorders

spasm and pylorospasm, the dyspepsia was too ill-defined to include with the ulcer group. There were two cases of sialorrhea whose underlying mechanisms were most consistent with the psychogenetic pattern outlined by Szasz.[24]

Forty-one syndromes were reflected in the cardiovascular sphere. In seventeen instances a neurocirculatory asthenia configuration[25] was noted. The picture in twelve cases was that catalogued as neurogenic hypertension.[26] These patients had relatively early, labile hypertension, antecedent and long-standing emotional difficulties, and exhibited the characteristics of "subnormal assertiveness" and "inhibited aggressiveness" which have been described.[27,28] Seven patients presented historical evidence of recurrent fainting compatible with vasodepressor syncopal attacks.[29] It was impossible to exclude, however, the possibility of hysterical mechanisms in these cases. Periodic headaches, migranoid in character, occurred in five women and correlated strikingly with episodes of emotional upset. Although their genesis may be speculated upon, they seemed to have been psychically precipitated.[30]

Musculoskeletal syndromes were noted in forty-six cases. The vast majority consisted of the so-called tension headache complex associated with the occipito-nuchal muscular component described by Wolff.[30] The remainder fell into small groups characterized by pain and discomfort stemming from tense, spastic musculature which in some cases was localized and in others was widespread. These individuals had all developed their complaints in a setting of emotional disturbance with their exacerbations also psychotemporally correlated.[31,32] They appeared to harbor a great deal of unexpressed anger and hostility and, physiologically, were "mobilized" for aggressive action which they had not initiated.

From Table VIII it will be seen that the overall sex ratio revealed a 2:1 female preponderance, as did the subtotals of the individual organ systems. There were but two areas with an equal sex distribution, neurocirculatory asthenia and the peptic ulcer-like syndrome. It is interesting that the three patients with x-ray evidence of ulcer were men.

In summary, and in contrast with the group O disorders, the current illnesses of group P were characterized by: (1) multiple complaints of a vague, often dramatic and bizarre nature; (2) ill health of insidious onset and lengthy duration; (3) gross objective evidence of emotional disruption mirrored physiologically by diffuse dysfunction and frequently accompanied by minimal or no primary organic disease; (4) many of the well known psychophysiologic syndromes; (5) a higher incidence in women.

THE ROLE OF PSYCHIC FACTORS

Tables IX, X and XI present in more detail various aspects of the psychic data. The high incidence of "psychopathy," the illnesses of 76 per cent of the total patient population having been significantly contributed to by psychic and psychophysiologic factors, is emphasized in Table IX. Two-thirds of these patients (49 per cent of the entire population) were suffering from psychogenic processes alone.

The remaining one-third (27 per cent of the total population) were "mixed" cases with both psychogenic and organic components in their illness. The former group contained a distinct preponderance of women while in the latter the men predominated.

TABLE IX
PSYCHIC FEATURES OF THE TOTAL PATIENT POPULATION (163 PATIENTS)

	Per cent	Ratio M:W
Incidence "psychopathy": *		
Total	76	4:5
Psychogenic only	49	3:5
"Mixed" †	27	3:2
Emotional stability:		
Stable	30	3:1
Unstable	48	4:5
Borderline	20	1:2
Unknown	2	...
Psychiatric consultation	26	2:3

* Psychogenic disorders
† Illnesses with both psychic and organic components

Table IX also presents an analysis of the basic personality integration, or emotional stability, of the entire patient population. This was achieved on the basis of the combined medical opinions and data from the social, economic, marital, medical and psychic histories. Only 30 per cent were adjudged stable, mature individuals with a 3:1 masculine preponderance. Conversely, 48 per cent were considered grossly unstable and immature; here the women predominated. Twenty per cent fell into a borderline category with many characteristics suggestive of long-standing instability but lacked sufficient evidence to label them, with complete assurance, as unstable personalities.

Thirty-five per cent of those patients with psychic factors in their illness (26 per cent of the total population) were seen in consultation by the psychiatrist. This had been considered for many more but was not feasible for various reasons. One group of patients, with little or no insight into the nature of their problems, were too "resistant" and vehemently rejected the recommendation. In other cases the additional time and expense involved proved prohibitive. The remainder were cooperative, well motivated patients with a variable degree of insight into their difficulties. They were deemed amenable to non-psychiatric management and, arrangements having been made for therapy by their home physicians, there was little purpose in psychiatric referral.

Table X is concerned with certain psychomedical features of the present illness of group P.

TABLE X
PSYCHOMEDICAL FEATURES IN THE PRESENT ILLNESS—GROUP P *

	Per cent	Ratio M:W
Role of psychic component:		
(a) causal and perpetuating	75	3:4
(b) secondary	19	1:1
(c) unrelated	6	3:1
Psychotemporal correlation	72	...
Illness used as solution	6	1:3
"Psychopathy" † complicated by organic disease	14	2:1
Medical errors:		
(a) mismanagement as somatic disease	23	1:3
(b) iatrogenicity	21	1:3

* Those patients with significant psychogenic disorders
† Psychogenic disorders

Emotional factors functioned as causal and perpetuating mechanisms underlying the present illness in 75 per cent of this group. The process was "somatopsychic" in 19 per cent, with the psychic manifestations having developed secondary to an organic process. Many, however, were basically unstable persons with emotional responses grossly out of proportion to the severity of the inciting organic disease. The remaining 6 per cent exhibited psychic features which appeared to arise from difficulties other than the present illness.

The onset of the current illness could be clearly correlated with some stressful life situation in 72 per cent of these patients. Although many were in truly desperate circumstances, the majority were simply over-reacting to relatively commonplace problems of life. Only 6 per cent appeared to be utilizing their illness, more or less unconsciously, to escape from or to solve some current difficulty with which they were otherwise unable to contend.

Fourteen per cent had developed organic disease superimposed upon a long-standing pattern of psychic dysfunction. These cases were usually puzzling as the structural process tended

to be distorted and camouflaged almost beyond recognition. Yet it proved important, and often vital, to detect the perhaps subtle organic infiltration amidst the maze of emotional manifestations. The early neoplasm and atypical myocardial infarction masquerading behind a neurotic exterior testified eloquently that "functional" and organic disorders are not mutually exclusive. The medical histories of these patients, nonetheless, strongly suggested that there persists a too common tendency to concentrate unduly upon one facet of a patient's problem. Consequently the danger exists that important structural lesions will be overlooked because the patient is "loaded with neuroses" or, conversely, significant psychic factors disregarded in favor of or misdiagnosed as organic disease. Twenty-three per cent of these patients, with a marked preponderance of women, appeared to have been mishandled in the latter manner. Another 21 per cent, mainly women, had been adversely affected by iatrogenic factors.[33,34] If these findings apply as widely as has been reported,[4,35,36] there is urgent need of general reorientation of medical attitudes and perspectives.

TABLE XI
EVALUATION AND PROGNOSIS OF GROUP P*

	Per cent	Ratio M:W
Severity "psychopathy"†		
(a) mild	21	2:1
(b) moderate	70	1:1
(c) severe	9	1:2
Tempo "psychopathy":†		
(a) acute	4	4:1
(b) chronic	88	1:1
(c) recurring	8	1:4
Attitude toward psychotherapy:		
(a) cooperative	64	3:2
(b) resistant	35	2:3
(c) unknown	1	...
Insight:		
(a) none	40	1:2
(b) superficial	53	1:1
(c) deep	4	1:4
(d) unknown	3	...
Type of psychotherapy required:		
(a) minor	66	5:4
(b) major	33	2:3
(c) unknown	1	...
Prognosis:		
(a) good	24	2:1
(b) fair	29	1:1
(c) questionable	29	1:2
(d) poor	15	1:1
(e) unknown	3	...

* Those patients with significant psychogenic disorders
† Psychogenic disorders

Table XI presents an evaluation of the psychic process, the type of therapy required and the probable prognosis of the group P patients. The severity of the "psychopathy" was graded mild in 21 per cent, moderate in 70 per cent and severe in 9 per cent. This differentiation was based upon the type of psychic disorder, its duration and the extent to which it had incapacitated the patient. The tempo was acute and of recent onset in 4 per cent, chronic and of lengthy duration in 88 per cent and, again chronic but characterized by recurring acute episodes in 8 per cent. The sex ratio in both these sets of data shifts from a masculine to feminine predominance parallel with increasing severity and duration.

Prior reference has been made to the "resistance" of some patients toward psychiatric help and their lack of insight into the role of emotional forces in their illness. As noted in Table XI, 64 per cent seemed willing to consult and cooperate with a psychiatrist when this was advised. Thirty-five per cent were obviously averse and, in some cases, bitterly hostile to this suggestion. A preponderance of women was again in evidence in the resistant group. Forty per cent had no appreciation of the psychic component in their problem while 53 per cent were aware, superficially, that their disturbed emotional state was somehow related. Only 4 per cent evidenced significant depth in their understanding of the nature of their illness.

An estimate of the psychotherapeutic requirements and prognoses was attempted for each patient in the light of the following factors: (1) the psychic aspect of the illness—its nature, severity, duration and significance to the patient; (2) the somatic component present—its nature, severity, duration, significance to the patient and probable prognosis; (3) the basic personality strength and emotional stability; (4) the degree of insight present; (5) the degree of motivation present; (6) the role of environmental and interpersonal factors; (7) the intelligence; (8) the age.

The resultant evaluations admittedly involve much conjecture, as complete data were unavailable in some cases and it was impossible to secure valid follow-up information in most by reason of their scattered residence. Nevertheless,

it was believed that 66 per cent required only "minor" therapy, such as could be provided by an understanding, interested, non-psychiatric physician.[37,38] For the remaining 33 per cent "major" therapy by a skilled psychiatrist was deemed necessary. In regard to prognosis, a good outcome was anticipated in 24 per cent. Two groups of 29 per cent each were regarded as fair and questionable, respectively. It was adjudged that 15 per cent would do poorly in spite of maximal therapeutic effort. As this prognostic breakdown indicates, superficial supportive therapy was not expected to "cure" all 66 per cent of the patients nor deep, expressive treatment the remainder. Cure, in the full sense of the word, was probably impossible for certain patients even with optimal psychiatric care. The evaluation pertained rather to the more realistic, often limited, therapeutic goals that might be attained by those patients with decreased psychic reserve. As we daily succeed in improving certain patients with decompensated rheumatic heart disease so may a certain proportion of our "stenosed" psychic cases be restored to a better, albeit sub-optimal, functional level. It was with this concept, and variable although limited goals in mind, that the therapeutic and prognostic estimations were made.

COMMENT

The stated purpose of this study was to evaluate the general and medical characteristics of a representative group of patients from the Private Outpatient Service of the Johns Hopkins Hospital with particular reference to the role of psychic factors in their illnesses.

The results of any clinical investigation must always be considered in the light of at least two cardinal components—the subjects investigated and the investigator.[39] It is recognized that the present subjects, 163 in all, comprise a relatively small group for statistical purposes and may not be truly representative of the POPS patient population as a whole. While admitting the statistical shortcomings, it is to be emphasized that this was a retrospective study, hence not capable of the often unconscious discriminations of a pre-planned effort. In addition, all patients were unselected, successive and routine assignments to the writer. In considering the investigator it is recognized that his special interest in this study pertained to psychic and psychophysiologic mechanisms as they related to medical problems. Although significant bias may have resulted therefrom, this criticism might be levelled generally, for most investigators delve mainly into fields of their special interest. There were two factors which tended to counterbalance any disproportionate emphasis—the writer is an internist concerned basically with internal medicine, not psychiatry, and, furthermore, the investigation and evaluation of each patient was carried out with the close collaboration and supervision of a senior medical consultant.

If then these patients are representative of the total clinic population, the data and analyses merit proportionate consideration.

The majority of the patients were in the third to sixth decade of life and, socio-economically, fell into the upper and upper middle class divisions delineated by Warner.[40] The medical problems were predominantly chronic in nature and infrequently severe enough to require hospitalization. The illnesses of 24 per cent (primary group I) were adequately explained on the basis of organic disease and significant emotional features were not detected. For the remainder (76 per cent) it was necessary to probe into the psychic sphere to evaluate completely and satisfactorily the various disorders. In 49 per cent of all cases the basic mechanisms were entirely psychogenic while in 27 per cent (primary groups III and IV) an admixture of psychic and somatic processes was present. This total incidence of "psychopathy" is almost identical with the 80 per cent reported by Roberts and Norton[7] whose patient group stemmed from a distinctly different socio-economic level. This would suggest that psychic factors are as prevalent and important in the medical outpatient clinic of a general hospital as they appear to be in a private diagnostic center. Robinson's findings[5,6] corroborate this as well in regard to the indigent group at the bottom of the socio-economic scale.

The analysis of the basic emotional stability and personality integration of these patients closely paralleled their final diagnoses. Only 30 per cent were adjudged to be mature, stable personalities with the remainder manifesting instability features, often of striking degree and usually of lengthy duration.

Despite the tendency of the psychogenic disorder to be reflected in multiple areas—social, occupational, economic, marital, sexual as well as medical—medical sins of omission and com-

mission seemed to have contributed significantly to the initiation and perpetuation of "dis-ease" in these, perhaps, vulnerable individuals.

Such mismanagement will continue if the tendency recently decried by Greer,[41] "to study the disease itself to the exclusion of its host—man," persists. His cogent advice to the physician to "view disease with the telescope as well as with the microscope" reaffirms the sentiments of Paul White,[42] who said: "Neither the psyche nor the soma should hold the limelight. They comprise but halves of the same circle, without beginning or end but with varying, alternating or even coincidental lengths of arc. We cannot well consider them separately. We must put the body together again . . ."

SUMMARY

An analysis of 163 unselected patients from a private outpatient clinic in a university hospital is presented. Their general and psychomedical characteristics have been evaluated in an attempt to delineate the kind of patient attending this clinic, the types of medical problems encountered and the role of psychic factors in these illnesses. It was determined in the patients studied that 49 per cent had psychogenic disorders alone and 27 per cent a combination of psychic and somatic processes. In all, 76 per cent of the patients were suffering wholly or in part from emotionally dictated disease. Their medical problems appeared to be merely one reflection of a multi-faceted personality disorder which was mirrored in many other spheres of activity. If these findings are valid and have widespread application, then, as physicians, we will have to pay more than lip service to the "person in the patient."[5]

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The Phenobarbital Sensitivity Syndrome*

THOMAS E. MCGEACHY, M.D. *and* WILLIAM E. BLOOMER, M.D.

Decatur, Georgia

THE fact that severe toxic reactions may occur following small dosages of phenobarbital is of great importance in view of the widespread use of this drug in general medical practice. These spectacular examples of idiosyncrasy are to be distinguished from those due simply to overdosage and from skin rashes following prolonged administration of large quantities, with cumulative effect, in which the reaction subsides on reduction of the daily intake.

In this report we deal specifically with a frequently fatal syndrome of hyperpyrexia, delirium and exfoliative dermatitis, with variably widespread parenchymatous organ damage, following ordinary therapeutic amounts of phenobarbital for a short period of time. Although such a symptom complex is undoubtedly of rare occurrence, early diagnosis is of prime importance in that prolonged administration of the offending agent may lead to a fatal outcome which perhaps could be avoided by more prompt recognition.

Examples of this type of reaction to phenobarbital have been reported by many observers. Hueber[1] in 1919 first reported a fatal case of "chronic infiltrating desquamating eczema" following the administration of phenobarbital. Chavany and Vannier[2] in 1929 reported a fatality in a thirty year old white female who had taken phenobarbital, gr. 1½ daily, for nine days. She developed exfoliative dermatitis, oliguria and high fever, and died on the sixth day of her illness. Severe congestion of the parenchymatous organs was the only finding at autopsy. Sexton, Pike and Nielson[3] reported a fatal case of exfoliative dermatitis following administration of 21 gr. of sodium phenobarbital parenterally, and 21 gr. of phenobarbital orally in a thirteen-day period. Scarlet and McNab[4] in 1935 observed a fatal termination in a patient who received 19½ gr. of phenobarbital over a period of thirteen days. Fever of 103°F., skin eruption of a macular and later bullous type, and coma were prominent signs. Other fatal cases have been reported by Lancaster,[5] Brunsting,[6] Millard,[7] Heckmann,[8] Wile and Benson,[9] Sweitzer and Laymon,[10] Poole[11] and Winer and Baer.[12] This brings the total reported fatal cases to fifteen to which we are adding two. In addition, we are reporting one case of apparent recovery.

Sweitzer and Laymon have reported two additional cases of fatal barbiturate idiosyncrasy following ingestion of barbiturates other than phenobarbital. The first of these was due to neonal (butyl-ethyl barbituric acid) with a hemorrhagic eruption, which terminated as granulocytopenia. The final leukocyte count was 250 cells per cu. mm. with no polymorphonuclear leukocytes seen. The second case report was that of a patient with dermatitis following the administration of sodium pentobarbital for ten days and was complicated by acute nephritis and a right lower lobar pneumonia. Unfortunately, permission for autopsy in both of these cases was not obtained. With the exception of these two questionable cases we have been unable to find examples of the fatal syndrome, which we have described, following administration of barbiturates other than phenobarbital.

CASE REPORT

CASE I. A. N., a Negro male approximately thirty-four years of age, was admitted to Grady Hospital on August 16, 1933. His chief complaint was an itching rash over his entire body. He stated that he had been well until the morning of August 14th at which time he had developed a headache while working in the sun. He obtained ten 0.25 grain tablets of phenobarbital from a friend and, due to their small size, he took six tablets, lay down under a tree and slept for four or five hours. On awakening his headache was still present so he went home to bed where he took the remaining four tablets. The next day he felt fairly well but began to notice itching and rash around his neck and

* From the Medical Service, Emory University Hospital, Emory University, Ga.

upper trunk. By the next morning the rash had spread over his entire body and he felt hot and feverish. A few blisters had also appeared on the palms of his hands. He was admitted to the hospital on the afternoon of August 16th approximately forty-eight hours after the ingestion of phenobarbital. There was no known previous ingestion of phenobarbital.

He was a well developed and well nourished male who appeared acutely ill. Temperature was 103°F., pulse 110, respirations 20 and blood pressure 124/76. There was a maculopapular rash over the entire body, including the palms and soles, which was rather confluent over the chest and face. On both palms there were several small bullae. The mucous membrane of the mouth was edematous and in the buccal mucosa there was one small clear blister. The remainder of the physical examination was essentially normal.

Laboratory studies on admission gave approximately normal results except for 1 plus albumin and a few red blood cells in the urine. During the course of the next four days he developed a progressive anemia and a mild leukocytosis. His albumin increased to 3 plus and there was gross hematuria. Blood non-protein nitrogen rose by the fourth day to 60 mg. per 100 cc. and creatinine to 4 mg. per 100 cc. Spinal fluid on the second hospital day was entirely normal.

Treatment was supportive. Wet boric acid dressings were applied to the exfoliative areas and he was given 1,500 cc. of 5 per cent glucose in normal saline twice daily. On the third hospital day he was given 500 cc. of whole blood. On the second hospital day his temperature had risen to 104°F. and he had become rather disoriented and confused. Mild diarrhea had also developed and he vomited several times. Bullae had appeared on the soles as well as the palms, and these rapidly increased in size. The entire mucous membrane of the mouth became edematous. Gross hematuria had developed. By the third hospital day his temperature was sustained at 104° to 105°F. and he was comatose. The mucous membranes of the mouth began to shed and there was some bleeding from the nose and oral cavity. There was exfoliation of the skin over the trunk and extremities, and almost a complete peeling of the skin on the palms and soles. Bleeding from the rectum had also become apparent. He remained in essentially the same condition during the third and fourth hospital days. By the fifth day he was exfoliating over his entire body with much outpouring of serum. He continued to bleed from his mouth and rectum and it was apparent that he was in extremis. By morning of the sixth hospital day his respiration was very shallow and labored, pulse was 160 and blood pressure was 70/50. On the afternoon of that day he expired. Permission for autopsy was refused.

CASE II. M. E. K., a twenty-seven year old white female, was admitted to Emory University Hospital October 12, 1947, complaining of skin rash and fever up to 103°F. of three days' duration. She had had chronic eczema involving her ears, which had become generalized involving her entire face, two weeks prior to admission. Patch tests had revealed positive reactions to paint and night face cream, and elimination procedures had been instituted. Five days prior to admission she began to take ½ gr. of phenobarbital three times daily, which she continued for forty-eight hours when she noticed a maculopapular skin eruption beginning on her right shoulder and becoming rapidly generalized, involving her trunk, face, arms and legs. The following day increasing fever, cervical adenopathy and periorbital edema were noted, along with irritative cough. On the day of admission her fever had risen as high as 103°F. and was associated with nausea, anorexia and vomiting. There was no history of previous hay fever, asthma, urticaria or use of phenobarbital.

On admission her temperature was 103°F., pulse 120, respirations 22 and blood pressure 100/60. She appeared to be acutely ill. An erythematous maculopapular rash was noted over her entire trunk, inner aspects of arms and upper thighs. The macular papules tended to coalesce over the chest but elsewhere were discrete. They faded but did not disappear on pressure. Cervical, axillary and inguinal lymph nodes were slightly enlarged and tender. Her face was puffy and an eczematous exfoliating dermatitis was found over the ears. The pharynx and palate were fiery red; the neck was supple. Examination of heart and lungs revealed no significant abnormality. The abdomen was normal and the spleen was not palpable. Rectal, pelvic and neurologic examinations revealed no abnormalities.

Urinalysis of specimens obtained by catheter revealed a heavy trace of albumin, 10 to 20 erythrocytes and 0–3 coarsely granular casts per high power field in a centrifuged specimen.

Specific gravity varied between 1.010 and 1.021 in three random specimens. Red blood cell count was 5.4 million cells per cu. mm. White blood cell count was 10,900 leukocytes per cu. mm. with 12 gm. of hemoglobin. Differential count revealed 2 juveniles, 16 stabs, 63 segmenters, 3 eosinophiles, 13 lymphocytes and 3 monocytes per 100 leukocytes. There were 35,600 platelets per cu. mm. Clot retraction began at forty-five minutes but was not complete in fifteen hours. Blood non-protein nitrogen, four days after admission, was 133 mg. per 100 cc., CO_2 combining power was 24 volumes per cent; total serum proteins were 5.5 gm. per 100 cc. with 3.5 gm. per cent albumin and 2.0 gm. per cent globulin. Spinal fluid examination the day after admission revealed 8 leukocytes per cu. mm. of which 56 per cent were polymorphonuclears and 44 per cent were lymphocytes. Total protein was 20.5 mg. per cent, sugar was 68.3 mg. per cent and chloride was 711 mg. per cent. Agglutinations for typhoid O and H, paratyphoid A and B, brucella and proteus OX19 were essentially negative on two occasions. Complement fixation tests for Rocky Mountain spotted fever and endemic typhus were negative. Two blood cultures revealed no growth. A moderate number of beta hemolytic streptococci were reported following throat culture.

Following admission, the patient continued to be febrile with continuous fever above 101°F. and spikes as high as 106°F. Frequent emesis and skin rash continued. Disorientation appeared after twenty-four hours and she continued to have delirium and hallucinations till her demise. Intravenous calcium gluconate, benadryl 50 mg. every four hours, and 40,000 units of penicillin every three hours did not seem to influence the course of the illness. On the third hospital day 6 mg. of paraminobenzoic acid was administered, without any appreciable effect except for moderate signs of acidosis with a CO_2 combining power of 24 volumes per cent which increased to 36 volumes per cent following administration of sodium bicarbonate.

In spite of oral and parenteral fluid intake between 2,500 cc. to 3,000 cc. daily, her urine output diminished progressively. Her eyelids and face became more edematous and, on the seventh hospital day, tracheal edema made tracheotomy mandatory. Her sensorium became increasingly clouded and at 9:00 P.M. of the seventh hospital day she expired following apparent respiratory paralysis.

An autopsy was performed which revealed edema of the glottis, gastrointestinal tract, bladder, retroperitoneal tissues, conjunctivae and kidneys. Small hemorrhages were noted in the tracheal-bronchial tree, skin, kidneys, stomach and oral cavity. The viscera were noted to be jaundiced, the liver was fatty and congestion of the spleen was observed. On microscopic examination collagenous degeneration of the corium of the skin was observed. The aortic valve was edematous along the line of closure, and scattered lymphocytes were seen in the subendocardial connective tissue and in the myocardium. A large area of recent hemorrhage was noted in the region of the atrioventricular node. The lungs revealed moderate interstitial and pulmonary edema with hyalinization of the walls of the alveolar septa. Section through an area of hemorrhage at the left apex revealed the alveoli to be full of blood, with intact walls. Small areas of pneumonia were noted. Massive edema of the stomach wall was noted. The liver showed evidence of a severe diffuse destructive process. In any given low power field less than 10 per cent of the tissue was recognizable as that of the liver. Most marked changes were in the mid-zonal or portal areas although the extensive parenchymal destruction made zone differentiation difficult. Cells in all stages of necrosis were observed. Recognizable liver cells were vacuolated and contained yellow pigment. Many mitotic figures were present.

CASE III. W. A. D., a forty year old salesman, was in good health until April 6, 1949, when he was administered phenobarbital, gr. 1 nightly for ten days, as part of symptomatic therapy for a perirectal fungus infection. There was no previous history of phenobarbital intake. Three days after beginning the drug he noted the onset of a diffuse erythematous rash on his face and trunk which progressed to involve the extremities and entire body except the palms and soles. Pruritus was fairly marked. Because of continuation of these symptoms he was admitted to Emory University Hospital on April 16, 1949, at which time he was having chills, fever up to 104°F. and severe sweats.

On admission the temperature was 101°F., pulse 90 and respirations 16. Blood pressure was 106/70. His entire skin was covered by a macular, slightly elevated rash with associated erythema which blanched on pressure. Scattered on his arms were several excoriated pustular lesions and a few small petechiae. Excoriations

were also noted about the buttocks and anus. The lymphatic system was normal. The mucous membranes were edematous with several bleeding areas. Several small petechiae were seen on the soft palate. There was injection of the umbo bilaterally on otoscopic examination. Examination of the eyes was not remarkable. His neck was normal. The chest was clear. A grade one apical systolic murmur was demonstrable. The abdomen was normal.

Urinalysis revealed a specific gravity of 1.015, pH 5.0, faint trace of albumin, no reducing substance, and occasional pus cell on microscopic examination. Hemoglobin was 13.1 gm.; the leukocyte count was 8,900 with 3 basophils, 81 polymorphonuclears, 12 lymphs and 4 eosinophiles on differential count. Two blood cultures showed no growth. A roentgenogram of the chest was interpreted as being within normal limits. The blood Kahn test was negative. There were no amebas in the stool.

He was given 100 mg. pyribenzamine every four hours and phenobarbital was stopped. His skin eruption rapidly faded and within forty-eight hours he became afebrile. On the fourth hospital day he was discharged and therapy discontinued.

On the second day after discharge the patient began to observe an erythematous skin rash, fever and malaise. He was given pyribenzamine 100 mg. every four hours without improvement. The following day nausea, vomiting and diarrhea became prominent symptoms and he was readmitted to Emory University Hospital on April 25, 1949. The temperature was 102°F., pulse 108, respirations 18 and blood pressure 104 systolic and 68 diastolic. A skin eruption, similar to that previously described, was observed. The skin between the buttocks was scaling and pigmented. There was no lymphadenopathy. The remainder of the examination was similar to that of the first admission. On urinalysis 8 to 12 pus cells and an occasional red blood cell was noted per high power field. Erythrocyte count was 3.65 million per cu. mm., and white blood count was 10,200 with 84 segmenters, 15 lymphocytes and 1 monocyte on differential. Hematocrit was 35 and sedimentation rate was 76 mm. per hour. A smear for malaria was negative. Two aerobic and one anaerobic blood culture revealed no growth. Stool culture grew out a non-pathogenic paracolon organism. Three fresh specimens were negative for amebas. Agglutinations for typhoid O and H, paratyphoid A and B, proteus OX19, tularemia and brucellosis were negative. Total serum proteins were 4.8 gm. with 2.4 gm. of albumin and 2.4 gm. globulin.

Pyribenzamine, 100 mg. every four hours, was administered with procaine-penicillin 300,000 units daily and intravenous fluids as needed. On the second hospital day his condition was deteriorating. He was hallucinated, confused and had continuous fever between 102° to 104°F. His blood pressure had dropped to 94 systolic and 60 diastolic. He was given 1 gm. of procaine intravenously in 1,000 cc. normal saline following which he seemed to improve somewhat, and his fever fell to 101°F. The following day his condition again became worse and aureomycin was given in dosage of 250 mg. every hour for 3 doses, then every two hours for 6 doses, then 500 mg. every four hours. His condition seemed unchanged. Daily procaine was given on the fourth and fifth hospital day at which time his fever began to fall by lysis, his rash began to fade and his mental symptoms to regress. By the eleventh hospital day his sensorium was clear and he was well except for a three-day recrudescence of fever of 99° to 101°F. from the twelfth to the fifteenth hospital day. He was discharged on the twenty-first hospital day at which time he was receiving 50 mg. pyribenzamine after meals and at bedtime.

He was given decreasing doses of pyribenzamine for the next six weeks, at which time all medication was discontinued and he continued to be symptom-free. In July, 1949, he was transferred to Houston, Texas, and soon after arriving there, according to a personal communication from Dr. Edwin M. Ory, he again developed fever, rash and swollen painful joints. He was again given pyribenzamine, 100 mg. every four hours, but did not appear to respond and, after approximately two weeks, the drug was discontinued, and he began to improve so that one week later he was again apparently well. As an experiment, he was again given pyribenzamine and, after three doses, his fever returned and his rash recurred but promptly disappeared when the drug was omitted. Since that time he has been symptom-free.

COMMENT

The similarity between these reported cases of phenobarbital sensitivity and others in the literature is quite remarkable in that a syndrome of erythematous rash, high fever, mental con-

fusion and toxic damage of parenchymatous organs occurred following minimal dosage of phenobarbital. A review of the literature reveals that similar reactions to the other barbiturates are extremely rare if they occur at all. It may be of some significance that phenobarbital (phenylethyl barbituric acid) is the only commonly used barbiturate containing a phenyl group. Conceivably, some abnormality in the metabolism of phenobarbital, in certain sensitive individuals, might liberate a phenol derivative producing diffuse cellular damage to the parenchymatous organs, as was strikingly observed in the second case in which necrosis of the liver cells was a prominent feature. The absence of any unusual damage to the blood-forming organs in any of our cases, as evidenced by demonstrable anemia, is in contradistinction to the usual picture of bone marrow depression typical of benzol poisoning.

The questionable response of Cases II and III to antihistamine measures would seem neither to establish or refute an allergic hypothesis. We are, however, impressed by what seems to be some evidence of response to intravenous procaine. The observation of a developed sensitivity to pyribenzamine with features similar to the original phenobarbital reaction in one instance would suggest that the original response was allergic in character.

In view of the fact that phenobarbital rightly enjoys wide clinical usage similar reactions will undoubtedly be observed. From our experience we believe that their management should entail careful attention to hepatic function. In view of the bleeding tendency observed in these patients hypoprothrombinemia may be a factor and, if present, the administration of vitamin K_1 oxide or similar substances might be of value. The use of human serum albumin is indicated if there is a fall in serum albumin. We believe that the use of intravenous procaine is indicated. ACTH or cortisone should certainly be tried in future instances of phenobarbital sensitivity. Unfortunately, these agents were unavailable during the time of study of our reported cases.

SUMMARY

1. A syndrome of fever, delirium, exfoliative dermatitis and parenchymatous organ degeneration following administration of therapeutic amounts of phenobarbital is reviewed.

2. Three additional cases of phenobarbital idiosyncrasy are presented, two fatal and one with recovery.

3. Possible etiologic mechanisms are briefly discussed.

4. The use of intravenous procaine and other suggestions for the management of future cases are presented.

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Seminars on Blood Coagulation

Allergic Purpura, Including Purpura Due to Foods, Drugs and Infections*

J. F. ACKROYD, M.B., M.R.C.P.

London, England

PURPURA is described as allergic when it results from an abnormal reaction either to an infection or to a food or drug or, occasionally, to some other substance. When purpura appears to be due to a factor other than an infection, the relationship can be proved by showing that the subsequent administration of the suspected substance, after the patient has recovered, results in a further attack of purpura. With regard to purpura which appears to be due to an abnormal reaction to an infection, the problem is complicated by the fact that it is not possible to provoke a further identical infection, and tests with autogenous vaccines have failed to cause recurrences of purpura.[40] For these reasons the relationship between an infection and an attack of purpura must be, in any individual case, a matter for conjecture, for there is clearly nothing to prevent the chance occurrence of these two conditions in the same patient without there being any aetiologic relationship. True purpura, when due to drugs or infections, differs from the majority of idiopathic cases in that it is, except when fatal, a disease of short duration characterized by complete recovery; and although purpura extremely rarely follows infections, it can be said that the association of this type of purpura with infections is too frequent to be due to chance. Consequently, it must be concluded that infections do, on rare occasions, cause purpura.

Classification of Allergic Purpura. Allergic purpura can be divided into two types: (1) Purpura which is associated with an erythematous exanthem and also with joint and visceral symptoms: the Henoch-Schönlein syndrome. This syndrome is conventionally classified with the allergic purpuras but in fact, apart from a very small proportion of cases which are due to foods and are truly allergic, the cause of the condition is unknown and its allergic origin entirely unproved. (2) True purpura, which is never exanthematous, i.e., the surrounding skin is normal. It may be caused by: (a) infections and (b) drugs (and occasionally certain other substances, possibly including foods in very rare cases). The mechanisms underlying purpura due to infections appear to be different from those underlying purpura due to drugs. They will therefore be dealt with separately.

The Fundamental Lesion in Purpura. Purpura is characterised by a tendency to bleed into the skin and mucous membranes which may show minute petechiae or extensive ecchymoses. Trivial injuries of the skin may bleed for long periods and there is often prolonged spontaneous bleeding from the mucous membranes. There may also be haemorrhages into the deeper tissues and internal organs. The capillaries in all types of purpura are abnormally fragile. This may be the only demonstrable lesion (athrombocytopenic purpura) or it may be associated with a marked decrease in the number of circulating platelets (thrombocytopenic purpura). In the Henoch-Schönlein syndrome the platelet count is normal or only slightly reduced, but purpura due to drugs or infections may be either thrombocytopenic or athrombocytopenic; moreover, the same drug or infection may produce either type of purpura in different individuals. It is important therefore to consider the relationship of thrombocytopenia to the capillary lesion, and the part played by these two factors in the causation of bleeding.

An increase in capillary fragility is of primary importance in the production of purpura for, clearly, haemorrhages cannot occur if the vascular endothelium is intact. Purpura does not occur even if the blood is temporarily rendered incoagulable by the use of heparin[189] nor, as Bingham and his co-workers have shown, does it occur in dogs in which a profound hypo-

* From the Medical Unit, St. Mary's Hospital Medical School, London, England.

prothrombinaemia has been induced with a single massive dose of dicoumarol. These workers, however, made an interesting observation which emphasizes the importance of the vascular lesion when they found that repeated smaller doses of dicoumarol did produce widespread haemorrhages even though they caused less depression of the blood prothrombin. These haemorrhages appeared to be due to vascular damage which was sometimes histologically demonstrable.[27,130]

The existence of a vascular lesion in purpura can usually be demonstrated by the positive pressure capillary fragility test of Hess[98] or the negative pressure tests of Hecht[94] or Scarborough.[182] In a commonly used positive pressure method[4] the arm is congested with a sphygmomanometer cuff placed above the elbow at a pressure of 80 mm. of Hg for five minutes, and the capillary fragility is estimated by observing the number of petechial haemorrhages produced in the congested area. The mechanism by which these petechiae are produced has been investigated by Humble[103] in a variety of different types of purpura, including anaphylactoid purpura and cases of thrombocytopenic and athrombocytopenic purpura due to hypersensitivity to drugs. The skin vessels were observed by capillary microscopy, and in every case investigated the haemorrhage occurred only from the arteriolar end of the capillary loop.

Very little is known of the nature of the vascular lesion in purpura. As a rule no vascular defects can be detected histologically[137] but Macfarlane,[133] who observed the nail fold capillaries in a large number of haemorrhagic diseases by capillary microscopy, showed that in both thrombocytopenic purpura and athrombocytopenic familial purpura the capillary loops were irregular and distorted. They were sometimes branched and, unlike normal capillaries, they failed to contract when punctured. He thought that these abnormalities probably accounted for the haemorrhages in these types of purpura.

Although there is general agreement as to the importance of the vascular lesion in purpura, great difference of opinion exists as to whether the thrombocytopenia, which is so frequently associated with purpura, plays any part in the development of the haemorrhages. It has repeatedly been shown that there is no constant relationship between the degree of thrombocytopenia and the severity of the haemorrhages. Severe purpura with normal platelet counts has been reported by many authors.[35,76,112,135,143,149,174] The converse, a low platelet count occurring in a patient without haemorrhagic symptoms, has also been reported.[31,54,176,190,198]

Similar findings have been observed in experimental animals. Thus thrombocytopenia induced experimentally with x-rays[121] or by "agar serum"[22] has failed to produce purpura, and severe haemorrhagic purpura with a normal platelet count has been produced in rabbits by the injection of streptococcal toxin.[166]

The frequent association of purpura with thrombocytopenia has, however, to be explained. So marked is this association that many authors[51,52,67,85,107] refer to a critical level for platelets below which purpura is likely to occur.

It has been suggested[199] that low platelet counts in purpura may be due to the endothelial damage, the platelets being used up in repairing breaches in the capillary walls. If this were so, thrombocytopenia should be a constant finding in purpura whereas, in fact, cases with normal platelet counts are considerably more common. Also, the healthy bone marrow can rapidly produce enormous numbers of platelets, as is shown by Duke's[50] experiments on platelet regeneration, and also by the rapid rise in the platelet count that frequently follows the induction of thrombocytopenia by the administration of a small dose of a drug to a patient who has recovered from an attack of thrombocytopenic purpura due to that drug.[1] It therefore seems improbable that the necessity for repairing endothelial damage can cause thrombocytopenia unless platelet formation is impaired.

Duke,[51,52] who noted a striking though temporary reduction in the haemorrhagic tendency in two cases of thrombocytopenic purpura when the platelet count was raised by transfusion, thought that thrombocytopenia itself was an important cause of the bleeding, and that haemorrhages occurred because insufficient platelets were available to repair defects in the capillary endothelium. Further evidence that the platelets are concerned with the maintenance of normal capillary permeability has been provided by Danielli[44] who has shown that the rate of development of oedema in the perfused hind limb of the frog can be greatly reduced by the addition of mammalian platelets to the perfusion fluid. He considered that the action of the platelets was largely

mechanical, involving simple blockage of protein-permeable pores in the capillaries.

Platelets liberate an intensely active vasoconstrictor substance during coagulation.[171,212] This substance is probably 5-hydroxytryptamine.[168] It is not present in thrombocytopenic blood.[170] It acts only on vessels with muscular walls and not on the capillaries.[169,213] The part played by this substance in normal haemostasis is uncertain. It is probably liberated from the blood which escapes into the tissues as a result of injury, and may well cause constriction of the muscle-coated vessels supplying the injured area, so reducing bleeding and allowing time for haemostasis to become established by the formation of a firm clot. Although the absence of this substance presumably cannot account for the haemorrhages that occur in thrombocytopenic purpura, it may conceivably result in a failure of constriction of muscle-coated vessels supplying areas of spontaneous capillary haemorrhage, and so increase the tendency to continued bleeding, with the production of ecchymoses and larger haemorrhages.

These observations show that thrombocytopenia may tend to increase the haemorrhagic tendency due to the vascular lesion but do not show why the two should so frequently be associated. For a further understanding of this problem reference must be made to the classical experiments of Bedson[22,23] which have been confirmed by Elliott and Whipple.[56] These workers not only showed conclusively that thrombocytopenia can increase the haemorrhagic tendency due to capillary damage but also that both these lesions may have a common cause. Bedson[22] first showed that if he reduced the number of circulating platelets in guinea pigs by the injection of "agar serum" no purpura resulted, nor did it occur if he injected anti-erythrocyte serum, which caused capillary damage but did not reduce the platelet count. He subsequently found that if he reduced the platelet count with "agar serum" after the capillaries had been damaged with anti-erythrocyte serum, purpura did occur. He concluded, therefore, that thrombocytopenia, by itself, was insufficient to cause purpura and that a damaged vascular endothelium was also necessary. Bedson[22] also found, however, that if he reduced the platelet count with anti-platelet serum, purpura occurred without the necessity for damaging the vascular endothelium with anti-erythrocyte serum. He explained this by the observation that anti-platelet serum, in addition to destroying the platelets of guinea pigs, also damaged the endothelium of the capillaries of these animals, and that after the administration of anti-platelet serum "the endothelium appears swollen and oedematous, the cells standing off the vessel wall." In a later paper the same author[23] showed that it was the vascular damage that was the important lesion in the production of purpura with anti-platelet serum. He found that it was possible so to grade the dose of anti-platelet serum in rabbits that the platelets could be destroyed without causing vascular damage and, consequently, without the occurrence of purpura; but that if a larger dose of serum was given, the capillary endothelium was also attacked, and haemorrhages developed. These experiments are of great importance for they imply a close antigenic relationship between platelets and the vascular endothelium and therefore suggest that any substance which causes vascular damage (and consequently tends to produce a haemorrhagic state) may also produce a reduction in the number of circulating platelets. Moreover, if it is accepted that platelets are formed from the cytoplasm of megakaryocytes, it would seem probable that this latter effect must result from injury to both the platelets and megakaryocytes, as it is difficult to imagine a factor so specific that it could injure either alone. These experiments are also important because of the very close resemblance of the syndrome produced by anti-platelet serum in guinea pigs and rabbits to a condition in man, namely, thrombocytopenic purpura due to hypersensitivity to the drug sedormid (allyl-isopropyl-acetyl-carbamide), in which it has been shown that there exists in the sera of patients who suffer from this form of hypersensitivity an antibody which, in the presence of sedormid, destroys platelets, and also damages the vascular endothelium.[1–3,5,6]

To summarize, the main lesion causing purpura is an increased capillary fragility, although the haemorrhagic tendency may be increased by a co-existent thrombocytopenia. The thrombocytopenia, when present, is probably due to the factor causing the capillary damage. This factor probably acts both on the platelets and the megakaryocytes.

THE HENOCH-SCHÖNLEIN SYNDROME

This syndrome, which is also known as anaphylactoid purpura, allergic purpura or

haemorrhagic capillary toxicosis, is characterized by three main groups of symptoms: first, lesions of a remarkably pleomorphic and usually purpuric type in the skin and mucous membranes; second, gastrointestinal symptoms, including intestinal colic, vomiting and sometimes intestinal bleeding; and third, pains in and around the joints. The syndrome used to be divided into three: purpura simplex, in which the purpuric skin lesions described below were the only symptom; Schönlein's purpura, or purpura rheumatica, in which the cutaneous manifestations were associated only with joint pains; and Henoch's purpura, or purpura abdominalis, in which the skin lesions and gastrointestinal symptoms were unassociated with joint pains. It is now realized that these are but different types of the same syndrome and that all three groups of symptoms may occur in the same patient. The name Henoch-Schönlein syndrome is preferable to the other titles which have been given to this condition as it does not imply any knowledge of its pathogenesis which, except for a small proportion of cases, is obscure.

The Henoch-Schönlein syndrome was first extensively investigated by Osler; and although some of his cases would not now be included under this diagnosis, his meticulous histories of numerous patients, many of whom he was able to observe for years, remain the most important available source of information about the disease.[155–159] Osler's cases have been admirably reviewed by Pratt.[164,165]

Clinical Picture of the Henoch-Schönlein Syndrome. The disease occurs more commonly in males than in females and is usually seen in children and adolescents although cases with predominantly arthritic symptoms are more common in young adults. No age is, however, immune.

In contrast with most other forms of purpura, haemorrhage in the Henoch-Schönlein syndrome is rarely severe, and purpura is often a relatively minor component of the syndrome, and in some attacks it may even be absent. The visceral symptoms, particularly the severe bouts of intestinal colic, or the arthritic symptoms more commonly dominate the picture.

The clinical story is remarkably variable. The onset may be with headache, anorexia and fever, or abdominal pain may usher in the attack. In other cases, pains in and around the joints are the first complaint, whilst in yet others the skin manifestations may be the first symptom, although these are often not noticed by the patient.

The course of the disease is characterized by a remarkable tendency to recurrences. A single attack seldom lasts more than a week. It may be only one or two days before the symptoms cease and the purpura begins to fade. Then, almost invariably, after an interval usually of days but sometimes of weeks or months, a further attack begins which again subsides, only to be succeeded by yet another. The attacks may closely resemble one another or may differ considerably. Thus, in some the skin may be normal and colic may be the most striking feature, whilst in others the skin lesions and joint pains may be the only symptoms, or the skin lesions may be associated with both abdominal and arthritic symptoms. The skin lesions may be similar in successive attacks or may differ strikingly. Although the average duration of the disease is of the order of a month, with about four or five recurrences, some cases go on for much longer as, for example, a patient mentioned by Pratt[164] who had over sixty attacks in five years. In some of Osler's cases symptoms recurred over even longer periods, and one of Davis'[45] patients had attacks at intervals for fifty years.

The following is a brief description of the individual components of the syndrome:

Fever. This occurs in less than half the cases. It is usually slight, although it may be up to 102°F. It usually lasts for less than a week and may be present only for a day or two. Very rarely a low grade fever may persist for several years.[45]

Skin Lesions. Purpura: This may be simple, the surrounding skin showing no change, or the purpuric lesions may be raised, in which case the petechial haemorrhages occur in the centre of an area of erythema. Purpura usually appears in crops, new lesions developing every few days. The distribution of the purpura is the same as that of the erythematous lesions described below.

Ecchymoses may also occur and these may be capped with bullae which sometimes burst to form open ulcers.

Urticarial wheals may occur at any stage of the disease. Haemorrhage sometimes occurs into the wheals. Itching is generally slight.

Oedema is common and may be extensive, even in the absence of renal involvement. It is often localized and transitory, resembling angioneurotic oedema.

Erythematous lesions: These are the most characteristic of the skin lesions of the Henoch-Schönlein syndrome. They resemble the lesions of erythema exudativum multiforme, and the fact that this condition may occasionally be associated with visceral and arthritic symptoms[136,165,178] gives strong support to Osler's view that the Henoch-Schönlein syndrome is a haemorrhagic form of erythema exudativum multiforme. This view has been strongly supported by MacLeod[136] who stated "This type of case (Purpura rheumatica) is identical with that referred to as Erythema haemorrhagicum, under the heading of Erythema multiforme exudativum."

The lesions are, at first, rounded papules. Although they may occur on any part of the body, they are most commonly seen on the extensor surfaces of the limbs and on the buttocks and lower part of the back. They seldom occur on the face. They tend to be symmetrical in distribution. They may sometimes be seen in the mucous membranes of the mouth and pharynx, and occasionally they are limited to the skin overlying the painful joints. The lesions are at first pink, later becoming red. At this stage they pale if compressed with a glass slide. Within twenty-four hours they generally become purpuric from extravasation of red cells into the centres of the lesions, which do not then pale when compressed. At this stage the lesions may no longer be raised and the erythema may have faded so that only the central haemorrhages remain, being now indistinguishable from the petechiae or ecchymoses of true purpura. The haemorrhages become purple and slowly fade through various shades of brown and yellow until by the end of about ten to fourteen days they have disappeared. Vesicles, into which haemorrhage may occur, sometimes form on the papules. The papules vary in size, the majority being from about a ¼ to 2 cm. in diameter, but much larger patches of erythema may occur. Rarely, there is a tendency to centrifugal expansion with central healing so that circinate lesions are produced. Occasionally, lesions indistinguishable from erythema nodosum may be seen.

As stated above, the skin lesions may differ from one attack to another. Several different types of lesion may be seen in the course of a single attack, and may even occur simultaneously. Photographs of a patient with typical skin lesions are shown in Figure 1.

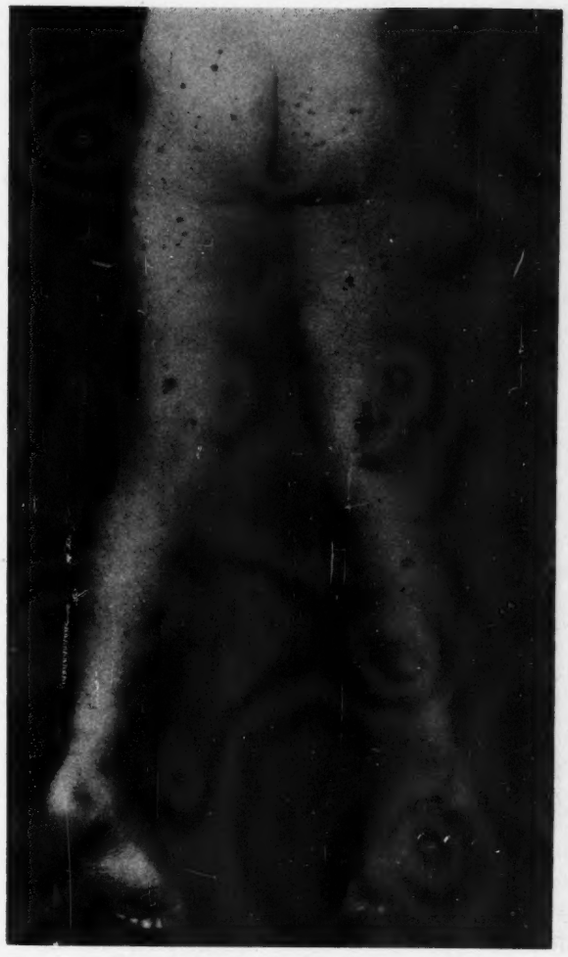


FIG. 1A. Henoch-Schönlein syndrome. Showing distribution of rash on buttocks and backs of legs. There were very few spots elsewhere.

Joint Symptoms. Joint pain is often the first manifestation of the syndrome but may occur at any stage of the disease. It is often associated with diffuse pain in the limbs. Several joints are usually involved in a single attack although the pain may, on occasion, be confined to a single joint. The knees and ankles are the joints most commonly affected. The pain may flit from joint to joint. Although it may be severe, the pain is rarely as intense as in acute rheumatism. The painful joints may or may not be swollen or tender. Swelling, when present, is apparently periarticular, and clinically detectable effusions into the joints are rare. The attack lasts only for a few days, after which the joints recover completely. There may be only one episode of joint pain throughout the whole illness but more commonly there is a marked tendency to recurrence of the pains.

Abdominal Symptoms. Abdominal pain of a



FIG. 1B. Details of rash behind the right knee in Figure 1A. The lesions are slightly raised. The illustration shows areas of erythema with central haemorrhage.



FIG. 1C. Ankles in Figure 1A showing periarticular oedema.*

colicky type is the most striking symptom of the Henoch-Schönlein syndrome. Although sometimes trivial it may be of great severity, causing the patient to roll about on the bed. The pain is generally in the umbilical region or, less commonly, epigastric or suprapubic. It may radiate to any part of the abdomen. The attacks are frequently associated with vomiting, the vomit sometimes containing blood. At the onset there is often obstinate constipation which may persist for days. In some attacks the patient passes blood and mucus per rectum. Sometimes there is frank diarrhoea and the stools may contain blood. After a few days, rarely longer than a week, the attack subsides. As with every other symptom in this disease there is a marked tendency to recurrence. Occasionally the attacks recur for years before the skin lesions appear and the condition then presents as one of recurrent unexplained abdominal pain. On examination of the abdomen during the attack there may be no abnormal physical signs. Sometimes an abdominal mass can be felt.[16] This, in the presence of severe colic, repeated vomiting and persistent constipation often leads to a diagnosis of acute intestinal obstruction. In some cases a diagnosis of acute appendicitis or of peritonitis[196] has been made. If bloody mucus is passed per rectum, or if the finger stall after a rectal examination is covered with blood, a diagnosis of intussusception is likely to be considered. In an enormously high proportion of cases, however, the pain subsides in a matter of hours or at the most a few days, and the patient recovers completely.

Many cases have been operated on unnecessarily. This has occurred particularly when the abdominal symptoms have preceded the skin lesions. In fact, no patient with atypical abdominal symptoms, or with symptoms suggesting intestinal obstruction, should be operated

* *Summary of history*—(reported by kind permission of Dr. Pearse Williams): D. S., girl age three and one-half years. 9/1/52: Onset with pain and swelling of ankles; rash began to appear about 2 hours later; Hess test negative; platelets 160,000/cu. mm; spots in rash of three types; simple purpura, erythematous papules with central haemorrhage, and erythematous papules with central vesicle. 9/3/52: Wrists swollen and painful; urticaria of forehead; urine normal. 9/4/52: Abdominal pain and vomiting; oedema of face; rash fading; haematuria, no casts. 9/6/52: A new crop of spots; left elbow painful and swollen. 9/7/52: Blood in stools; still has haematuria, no casts; no abdominal pain; facial oedema and joint pains less. 9/8/52: Has stopped vomiting; no new spots; urine-slight albuminuria, no casts. 9/11/52: Some new spots on legs; there is blood in stools. 9/15/52: Further attack of abdominal pain and vomiting; oedema of right side of face, 9/17/52: Appears well; a few fading spots only; urine normal. 9/19/52: Slight attack of abdominal pain; no vomiting. 9/21/52: Appears well; stool: passed one fresh blood clot. 9/24/52: Well; urine normal. 9/29/52: Discharged.

on without inquiry being made for previous attacks of purpura and joint pains, a search being made for skin lesions, and the urine being examined for red cells. The capillary fragility and the reaction of the skin to slight local trauma should also be investigated.[19] Even then it must not be forgotten that the Henoch-Schönlein syndrome is an occasional cause of intestinal obstruction, usually from intussusception, and it is inevitable that in a certain number of cases laparotomy will be performed although no lesion amenable to surgery may be present. The lesion most commonly found at operation is an extravasation of blood or serosanguineous fluid into the wall of the small intestine. The illustration (Fig. 2) shows the appearance in a case operated on by Bailey.[16] The lesion was a subserous extravasation of blood affecting about 4 feet of jejunum. The gut was not resected and the patient recovered. Such an extravasation of blood, occurring into the wall of the gut, may rarely cause intestinal obstruction.[16] Intussusception occurring in the course of the Henoch-Schönlein syndrome is probably due to haemorrhage or extravasation of serosanguineous fluid into the submucosa which then protrudes into the lumen of the gut, thus provoking intussusception. Local extravasations may produce haemorrhagic ulcers in the wall of the gut.[81,196] These may rarely perforate.[81]

Bleeding from Other Sites. Epistaxis and bleeding from the gums may occur but are much less common than in true purpura.

Symptoms Referable to the Central Nervous System. Transient pareses and epileptiform convulsions have been recorded as extremely rare complications of the Henoch-Schönlein syndrome.[84,159] Subarachnoid haemorrhage[87] and cerebral haemorrhage[159] have also been reported.

Renal Complications. Haematuria is common and may have no greater significance than bleeding elsewhere. Microscopic haematuria occurs in the majority of cases at some stage of the disease. Nephritis is the most serious complication of the Henoch-Schönlein syndrome. The majority of cases recover. The condition appears to be indistinguishable from Type I nephritis of Ellis.[57]

Splenomegaly. Occasionally the lower pole of the spleen can be felt on abdominal examination.

Special Investigations. Blood: There are no striking changes. Haemorrhage is rarely sufficient to produce more than a very mild anaemia. A polymorphonuclear leukocytosis has sometimes been reported and there is occasionally an eosinophilia. The platelets are normal or only slightly reduced in number. Bleeding time, coagulation time and clot retraction are normal.

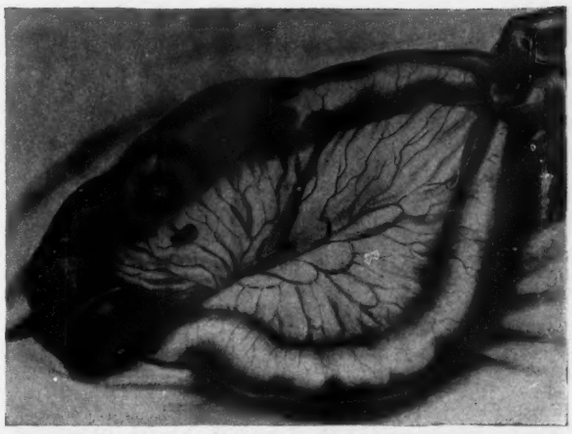


FIG. 2. Henoch-Schönlein syndrome. Drawing of the findings at operation in a boy of eight with a purpuric rash and signs suggestive of intestinal obstruction. An ill defined mass was palpable immediately above the umbilicus. The lesion found at laparotomy was a subserosal extravasation of blood affecting about 4 feet of jejunum. There was no intussusception or obstruction. The gut was not resected and the patient recovered. Redrawn by Miss Treadgold from Bailey, H. (*Brit. J. Surg.*, 18: 234, 1930) by courtesy of the author and publishers.

Capillary fragility: The capillary fragility tests produce petechial haemorrhages in some cases only. According to Pratt[165] the positive pressure tests may sometimes cause urticarial wheals in the congested area.

Bright red lesions may appear twelve to twenty-four hours after slight local trauma to the skin. They can sometimes be produced between attacks when the skin appears entirely normal. They slowly fade, as do the erythematous lesions of the Henoch-Schönlein syndrome. Such lesions may be provoked by firmly stroking the skin with a blunt rod and they may appear in the skin compressed by the sphygmomanometer band used for the positive pressure capillary fragility test. They may also be provoked by any intradermal injection and may therefore cause a Mantoux or other intradermal test falsely to be read as positive.[70]

Pathology. The skin: The histology of the erythematous lesions has recently been investigated by Gairdner.[70] He claimed that these lesions have a specific histology found only in the Henoch-Schönlein syndrome and in the skin lesions of acute rheumatism. It is, however, clear from the studies of Unna[201] and MacLeod[136] that the histology of the skin lesions as described

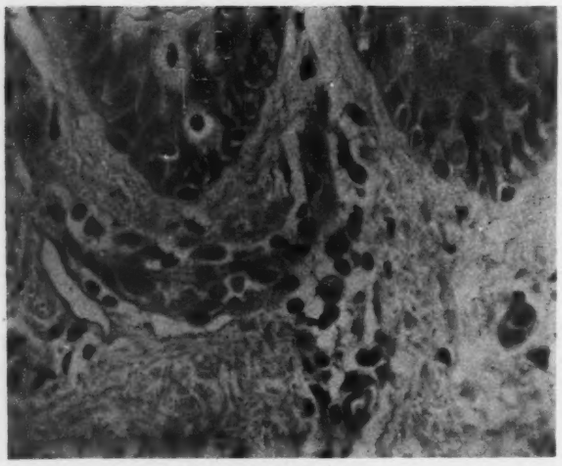


FIG. 3. Section of a small erythematous papule from patient D. S. whose skin lesions are shown in Figure 1. The section shows a small dilated papillary vessel with a perivascular infiltration of polymorphonuclears and histiocytes. The endothelium of this vessel is normal but other capillaries in the same section showed endothelial swelling. × 400.

by Gairdner bears a sufficiently close resemblance to that seen in erythema exudativum multiforme to suggest a close relationship between the two conditions.

Section of the erythematous lesions of the Henoch-Schönlein syndrome shows an inflammatory infiltration around the small vessels of the corium. The predominant cells are polymorphs and histiocytes. There may be appreciable numbers of eosinophils. There are also collections of red cells in the perivascular tissues. The vessels are dilated but their endothelium usually appears normal, although there may be some endothelial swelling. The epidermis may be oedematous and sometimes shows minute bullae into which haemorrhage may occur. The unaffected skin is histologically normal.[70] The histologic appearance of a typical lesion is shown in Figure 3.

The other skin lesions, simple purpura, urticaria etc. are macroscopically indistinguishable from similar lesions occurring in other conditions. There do not appear to be any adequate histologic studies of these lesions in the Henoch-Schönlein syndrome.

Other tissues: The Henoch-Schönlein syndrome is rarely fatal and there are very few postmortem reports. There appear to be no reports on the changes in the joints. The scanty literature on the pathology of the kidneys in cases with nephritis has been reviewed by Gairdner.[70] Most of these cases were described as subacute or chronic nephritis and do not appear to have shown any striking differences from these conditions as seen in Type I nephritis of Ellis.[57] The gross appearance of the lesions in the intestines, as studied at operation, has been described above. Sturtevant and Graef[196] made numerous sections of an extensive haemorrhage into the wall of the ileum from a patient with the Henoch-Schönlein syndrome. They found no vascular changes.

Diagnosis. The association of purpuric erythematous skin lesions with visceral or arthritic symptoms in a patient with a normal platelet count usually makes the diagnosis easy. The diagnosis of cases with abdominal symptoms only and of cases with intestinal obstruction has already been discussed.

Occasional cases have been reported in which polyarteritis nodosa has exactly mimicked the clinical picture of the Henoch-Schönlein syndrome.[117,191] Biopsy of the skin lesions in such cases should make the diagnosis clear.

In the condition known as purpura simplex, the purpuric erythematous skin lesions described above are the only symptom,[92] although a careful history will often reveal minor abdominal or joint pains. The erythema and swelling of the lesions in some very mild cases may disappear rapidly, leaving an apparent true purpura, but observation of successive crops of the eruption should reveal its erythematous origin. Cases of true purpura in which the haemorrhages are confined to the skin and the platelet counts are normal should not be described as purpura simplex and should not be classified with the Henoch-Schönlein syndrome.

It is most important that every case of the Henoch-Schönlein syndrome which runs a persistent course should be investigated from the point of view of food allergy because, as mentioned below, there is unequivocal evidence that the syndrome may very occasionally be due to hypersensitivity to certain articles of food. The history may suggest this diagnosis and the relationship of the suspected substance to the symptoms can then be investigated by making the symptoms disappear, and then reappear, by removing the suspected article from the diet and subsequently giving it again. Cooke[40] has suggested that no case of food or drug idiosyncrasy should be considered proved unless the same lesion or lesions have been produced on at least three occasions at the same time interval after the administration of the suspected sub-

stance. If such a rule is not followed, mistakes are bound to occur.

If food allergy is suspected as the cause of the syndrome but the history does not reveal the identity of the offending substance, the patient should be instructed to keep a diary of foods eaten. When he has had several further attacks it may then be possible to identify the cause. If this does not succeed, Rowe's[177] "elimination" diets may be tried in the hope that the symptoms will disappear when the patient is receiving one of these diets. Finally, if all else fails, the patient can be put on a diet of glucose and water. If the symptoms do not disappear within a few days it is unlikely that the condition is due to food allergy. If they do, or if they disappear with Rowe's diets, further articles of food may be added slowly until the symptoms reappear, and in this way the cause can be found. Skin tests are seldom of help in the diagnosis of this type of case.

Treatment. The majority of cases clear up in about a month and require only symptomatic treatment. In the more chronic cases, apart from the elimination of the offending article of diet in the very rare cases due to food allergy, there is no satisfactory treatment. Foci of infection should be dealt with on general principles; but although such lesions have frequently been stated to be the cause of the syndrome, their treatment usually has no effect on the course of the disease. Adrenocorticotrophic hormone (ACTH) has been tried with equivocal results.[193] Nephritis is the most serious complication and, in view of Ellis'[57] observation that the chances of recovery are greatly improved if patients with acute nephritis are nursed in bed, it seems reasonable to keep all patients with the Henoch-Schönlein syndrome in bed in the hope that this may reduce the incidence and severity of nephritis.

Pathogenesis. Cause of haemorrhages in Henoch-Schönlein syndrome: The haemorrhages that occur into the erythematous lesions are probably due to the same process that causes the erythema, the red cells escaping from the dilated capillaries.

The cause of the purpura in apparently normal skin is uncertain. Microscopic examination of the nail fold capillaries in the living subject has usually failed to reveal any abnormalities.[70,134] Frank[68] maintained that purpura in apparently normal skin is always the residue left behind by a fleeting erythematous rash. If this is true, these haemorrhages must presumably also be due to the same process that causes the erythema.

The rôle of infection: It has for long been believed that the Henoch-Schönlein syndrome is a manifestation of bacterial allergy and is caused particularly by streptococcal infections, although other infections, especially tuberculosis,[21,42] have also been considered. The evidence is, however, inconclusive and both Pratt[165] and Cooley[41] have denied that infection is a cause. Such evidence as there is may be briefly reviewed as follows:

1. Cases in which treatment of an infection has coincided with recovery from the disease: Bradburn[30] has reported a dramatic example of this and Rosenthal,[175] Kugelmass[115] and Burnet[36] have had similar experiences. It is, however, difficult to draw conclusions from evidence of this type in a condition like the Henoch-Schönlein syndrome which has such a marked tendency to spontaneous recovery. Moreover, in three of Gairdner's[70] cases which had streptococcal throat infections, penicillin failed to produce any improvement, and in one of these cases, in which the syndrome was associated with a chronic purulent tonsillitis from which a heavy growth of haemolytic streptococci was repeatedly obtained, tonsillectomy, although it cleared the throat of streptococci, had no effect upon the course of the syndrome.

2. Cases occurring after streptococcal infections: The Henoch-Schönlein syndrome may occur following scarlet fever[29,65,188] and ten of Davis'[45] forty-four cases of the syndrome were preceded by acute tonsillitis. This author, however, found normal antistreptolysin titres at the height of the disease in six of eight of his cases.

3. The frequency of streptococcal throat infections in patients with the Henoch-Schönlein syndrome: Gairdner[70] found haemolytic streptococci on two or more occasions in the throats of five of twelve patients with the Henoch-Schönlein syndrome but only in one of ten control patients in the same wards. He also observed that streptococcal infections occurring during the course of the syndrome generally provoked relapses or exacerbations, an observation also reported by Coke,[38] Davis[45] and Kugelmass.[115]

That the co-existence in the same patient of an infection and the Henoch-Schönlein syndrome may not be aetiologically significant is shown conclusively by a case described by Eyermann.[58] This patient had chronically infected tonsils and several apical dental abscesses.

The tonsils were removed and the abscesses drained with no effect upon her symptoms. It was then discovered that she always developed the syndrome whenever she took certain foods. Egg, chicken and beans consistently produced purpuric spots, abdominal pain and headache. Fish and lamb also caused abdominal pain and headache but no purpura. Only minute quantities of these foods were required to produce symptoms. Withdrawal of these foods from the diet resulted in complete recovery.

It can only be concluded that although streptococcal infections are common in patients with the Henoch-Schönlein syndrome, proof of a causative relationship is lacking.

The rôle of food allergy: It has already been mentioned that hypersensitivity to food may cause the Henoch-Schönlein syndrome. The earliest report of this association appears to be that of Galloway[71] who in 1903 described a girl who developed exudative erythema with purpura, bloody diarrhoea and haematuria every time she ate blackberries and nuts. This type of case is rare and a search through the literature has revealed only a small number of further examples, the better attested of which are summarized, with Galloway's case, in Table I. Although few of these cases were subjected to Cooke's[40] rigorous criteria, they were all investigated on at least one occasion by the administration of the suspected substance, with the production of purpura and generally one or more of the other symptoms of the Henoch-Schönlein syndrome. In every case removal of the offending food from the diet was followed by cessation of the symptoms. From this table it will be seen that egg, milk, chocolate, wheat and beans have been most frequently implicated, with a large variety of foods as occasional causes.

In conclusion it may be said that the cause of the vast majority of cases of the Henoch-Schönlein syndrome is unknown. Although the condition is widely believed to be a manifestation of allergy, this is entirely unproved except for the very small proportion of cases which appear definitely to be due to hypersensitivity to food.

PURPURA DUE TO INFECTIONS

The relationship of the Henoch-Schönlein syndrome to infection has already been discussed. Purpura of other types associated with infections may be classified as follows:

1. Conditions in which purpura is a part of the usual clinical picture of the disease, e.g., septicaemia.

2. Cases with a haemorrhagic rash: The infection in these cases is invariably severe. The haemorrhages are confined to the rash and appear to be due to the abnormal intensity of the process that causes the exanthem.

3. Cases of the haemorrhagic forms of the acute infections: These are extremely rare and very little is known about them. Some appear to be due to a secondary streptococcal septicaemia.[4]

4. Purpura fulminans: This is an extremely rare condition which was first described by Henoch.[96] It occurs chiefly in children and is characterized by extensive symmetrical ecchymoses. It is nearly always fatal within a few days. The skin vessels appear to be the only vessels involved. There is no bleeding from mucous membranes and the platelet count is normal. It most commonly occurs during convalescence from scarlet fever[55] and appears to be closely related to another extremely rare condition, post-scarlatinal gangrene, for the two conditions may occur simultaneously in the same patient.[55] Very few cases have been adequately investigated. Some have appeared to be related to the Henoch-Schönlein syndrome[69,70,78] but Gasser and de Muralt[72] have recently described two cases with a deficiency of factor V of Owren,[160] one of which also had an excess of antithrombin in the blood. It is clear that insufficient is known about this condition to permit any discussion of its pathogenesis.

5. Cases with which this paper is concerned: In these purpura occurs as a rare complication of an infection. It appears to bear no relationship to the severity of the primary disease and may complicate mild or severe infections. It has been reported most commonly following scarlet fever.[12,15,29,65,75,150] Cases have also been described following infectious mononucleosis,[13,125,138] varicella,[37,197] rubella,[4,66,77,88,139,163,205] diphtheria,[15,73,101,172,179] measles,[118,145,146] vaccinia,[184] catarrhal jaundice,[9,211] tuberculosis,[74,110,154,174,207,209] malaria,[187] brucellosis,[141] acute mastoiditis[152] and an acute upper respiratory infection.[64]

In considering these reports it should be noted that a few of the cases had received treatment before the purpura appeared, but in none were the drugs given again, after recovery, in order to show that they had not been the cause of the haemorrhages. Moreover, a small number

TABLE I

CASES OF THE HENOCH-SCHÖNLEIN SYNDROME DUE TO HYPERSENSITIVITY TO FOODS

Author	Case No.	Foods Causing Syndrome	Symptoms Produced by Administration of Causative Food						
			Purpura	Erythema	Urticaria	Blood in Stools	Haematuria	Colic	Joint Pains
Galloway (1903)	1	Blackberries and nuts	+	+	..	+	+	..	..
Sachs (1916)	1	Anchovy paste	+	..	..	..	..	..	..
Alexander and Eyermann (1927)	2	Milk	+	..	..	..	..	+	..
	3	Egg	+	..	..	..	..	..	+
Alexander and Eyermann (1929)	1	Milk	+	..	..	..	..	+	..
	2	Egg, potato and wheat	+	..	..	..	..	+	..
	3	Egg, chicken and beans	+	..	..	..	..	+	..
	4	Plums	+	..	..	..	..	+	..
	5	Wheat	+	..	..	..	..	+	+
	6	Pork, onions and strawberries	+	..	..	..	..	+	..
Barthelme (1930)	1	Wheat	+	..	..	..	..	..	+
		Egg yolk	+	..	..	..	..	+	..
Eyermann (1935)	1	Egg, chicken and beans	+	..	..	..	..	+	..
		Fish and lamb	..	..	..	..	..	+	..
Diamond (1936)	1	Milk	+	..	..	..	..	..	+
	2	Tomato and chocolate	+	..	..	..	..	+	..
	3	Popcorn	+	..	..	..	..	..	..
	4	Egg	+	..	..	..	..	..	..
	6	Chocolate	+	..	..	..	..	..	..
	7	Chocolate	+	..	..	..	..	..	..
	8	Chocolate	+	..	..	..	..	..	..
	9	Rolled oats and chocolate	+	..	..	..	..	..	..
Hampton (1940)	1	Milk	+	..	..	+	..	+	+
		Potato	+	..	..	+	..	+	..
	2	Carrot, milk, wheat, pineapple, apple, orange, prune and string beans	+	..	..	..	..	+	+
Brown (1946)	1	Tomato	+	..	+	+	+	+	+

of the cases developed respiratory tract complications such as otitis media, bronchitis, etc., before the onset of the purpura. Bacteriologic investigations were inadequate but it is clear that most of these complications must have been due to secondary infections which, although slight, might have been responsible for the purpura. Also, it must be remembered that, as has already been stated, it is impossible in any individual case to prove the relationship between purpura and an infection. Nevertheless, the occurrence of a brief episode of purpura, followed by complete recovery, in a patient who has never had any haemorrhagic symptoms before and who is suffering from, or who has recently recovered from an infection, constitutes strong presumptive evidence that the purpura was due to the infection. In so far as this is true it would seem likely that most of the cases listed above were due to the infection to which they were attributed and therefore that, although an individual case report may be misleading, it is justifiable to observe the general trends of the changes reported in these cases in order to build up a clinical and pathologic picture of the condition, and to endeavour to formulate a hypothesis as to the mechanisms underlying this type of purpura.

Incidence of Purpura Following Infections. The rarity of purpura following infections is indicated by the fact that Box[29] was able to find only about fifty cases following scarlet fever in the literature up to 1933. Frödin[69] has reported six cases of purpura in approximately 23,000 cases of scarlet fever, and Hunt,[104] two in 5,000 cases of scarlet fever, one of which was a case of streptococcal septicaemia. Purpura occurs even less frequently after other infections.

Clinical Picture. The picture varies from that of a small number of cutaneous haemorrhages during convalescence to the most fulminating purpura with extensive cutaneous and subcutaneous haemorrhages, and bleeding from mucous membranes, including epistaxis, bleeding from the gums, haematemesis and melaena. Haematuria is common in such cases and death may occur from haemorrhage into a vital organ. In cases which are not fatal the disease runs a short course and recovery is rapid and complete. There is no residual haemorrhagic tendency.

The purpuric eruption is never exanthematous, that is, it is a true purpura, the surrounding skin being normal and showing neither hyperaemia nor urticaria. The platelet count may be normal, slightly or moderately reduced, or there may be marked thrombocytopenia. In the cases listed above both thrombocytopenic and athrombocytopenic purpura occurred after scarlet fever, varicella, measles, tuberculosis and catarrhal jaundice, but the great majority were thrombocytopenic. It is difficult to assess the incidence of cases with thrombocytopenia because these, for reasons mentioned above, are usually the more severe, and therefore are more commonly reported. According to Box,[29] athrombocytopenic cases are much the commoner following scarlet fever, and this is probably also true of other infections.

The interval between the onset of the infection and the appearance of purpura varies considerably. In scarlet fever, for instance, purpura occurs most commonly in the third or fourth week[29] but may occur earlier or later than this, and in the case described by Fox and Enzer[65] purpura appeared at the end of the first week of the disease. In diphtheria, purpura has been reported as early as the first day of the disease[101] and as late as the twenty-fourth,[172] and in rubella, as early as the first day[163] and as late as the eleventh day after the appearance of the rash.[4] In general, it may be said that purpura may occur in the acute stages of an infection, or well on in the period of convalescence.

It was stated above that the incidence of this type of purpura bears no relationship to the severity of the primary infection. It has in the past been widely held that purpura occurs only in severe infections but this is clearly not correct. Thus in the three cases of thrombocytopenic purpura following rubella described by the author[4] the attacks of rubella were all very mild. Box[29] has stated that purpura complicating scarlet fever usually follows mild or only moderately severe attacks. According to Ker,[179] although the throat symptoms in cases of diphtheria which are complicated by purpura are usually severe, they are not necessarily so, and Gee[73] observed that purpura following diphtheria bears no relationship to the severity of the throat infection, and that the symptoms of diphtheria may be so slight that the diphtheritic origin of the purpura may be overlooked. A case of this type has been described by Howard.[101]

Blood Picture. Apart from the changes caused by the infection itself, the blood changes in purpura due to infections are identical with those seen in purpura due to drugs. Haemorrhage is often sufficiently severe to produce profound

anaemia. The white cells may be normal or there may be a polymorphonuclear leukocytosis. The platelet count may be normal or only slightly reduced or there may be extreme thrombocytopenia. The bleeding time is prolonged. In thrombocytopenic cases the coagulation time may be slightly increased and clot retraction is reduced in proportion to the reduction in the platelet count.

Pathology. Vessels: There appear to be no histologically demonstrable abnormalities in the blood vessels in this type of purpura.

Spleen: No significant abnormalities have been noted in the spleen in purpura due to infections other than tuberculosis. In some cases of tuberculosis the spleen is extensively involved, either as part of a generalized tuberculous infection or in the condition known as splenic tuberculosis,[209] in which the spleen is almost the only organ affected, the primary lesion having healed. Cases of either type appear sometimes to cause persistent purpura. The purpura has generally been thrombocytopenic[74,110,207] but cases of purpura with normal platelet counts have been reported.[154] Both thrombocytopenic and athrombocytopenic cases can be cured by splenectomy.[74,110,154,207] What proportion of cases of purpura associated with tuberculosis are due to splenic involvement is unknown, and the mechanism by which this type of purpura is produced is entirely obscure. There is no evidence that the spleen plays any part in the causation of purpura due to other infections.

Bone marrow: A wide variety of changes has been reported in the bone marrow in thrombocytopenic purpura due to infections. Gross morphologic changes in the megakaryocytes have been described in cases secondary to diphtheria[15] and septicaemia,[113,120] and in a case secondary to pulmonary tuberculosis these cells were so greatly reduced in number that examination of several marrow films failed to reveal any megakaryocytes or megakaryoblasts.[120] According to Leitner[120] the megakaryocytes in purpura due to infections are usually reduced in number and show degenerative changes. Such changes may well be sufficient to account for the thrombocytopenia. In cases following scarlet fever[150] and acute mastoiditis,[152] however, the megakaryocytes showed only hyperplasia, while the bone marrow has been reported as being normal in cases secondary to an acute upper respiratory infection,[64] infectious mononucleosis[125] and rubella.[4]

The cause of the thrombocytopenia in cases of purpura secondary to infections is uncertain. The observation that there is in some cases sufficient damage to the megakaryocytes to account for the thrombocytopenia suggests that the low platelet counts in those cases in which the megakaryocytes appear normal may have a similar cause, but that in these cases the injury to the megakaryocytes is insufficient to produce morphologically detectable changes. In many cases of thrombocytopenic purpura secondary to infections recovery is extremely rapid, and for this reason it is perhaps not to be expected that these cells should always show morphologic changes, although the damage produced may be sufficient to inhibit platelet formation. Injury to the circulating platelets probably contributes to the thrombocytopenia because, as stated above, any factor which causes injury to the megakaryocytes will probably also affect the platelets.

Diagnosis. The difficulty of establishing a relationship between purpura and infection has already been emphasized. Recovery from purpura due to infection is usually rapid and complete. If recovery does not occur or if there is a residual haemorrhagic tendency, it is probable that the patient is suffering from chronic purpura and that the infection has stimulated an exacerbation of the symptoms. Mills[146] mentions several cases of this type, and the patient with infectious mononucleosis and purpura described by Dameshek and Grassi[43] would appear to have been a further example. Alternatively, the patient may be suffering from the extremely rare condition of purpura due to tuberculosis of the spleen. The diagnosis of this condition presents great difficulties, especially in cases without evidence of tuberculosis elsewhere, and the majority of such cases have been regarded as examples of chronic thrombocytopenic purpura, the diagnosis being made only after the spleen has been removed. This diagnosis should be considered in any case in which persistent purpura is associated with tuberculosis, even though the infection may be slight in extent and may appear inactive.

Treatment. Apart from the treatment of the infection when this is still active, treatment is entirely symptomatic. Blood transfusions may be necessary in severe cases.

In cases which run a prolonged course the diagnosis of chronic purpura with a coincidental infection, or of tuberculosis of the spleen, should

be considered, and if purpura persists after repeated transfusions, splenectomy should be undertaken.

Pathogenesis. Any attempt to explain the mechanisms underlying this type of purpura must take into account three important points: (1) Purpura, even when due to the same type of infection, may be thrombocytopenic or athrombocytopenic. (2) Purpura may occur in connection with mild or severe infections. (3) Purpura may occur at the height of an infection or during convalescence.

At the height of almost any infection, including even the common cold,[18] there is a fall in the platelet count generally associated with a rise in capillary fragility. In considering the fundamental lesion in purpura it was shown that both these phenomena may have a common cause and it seems likely that this is true of these changes when they are due to infections, although the cause presumably varies with the primary disease. In investigating these changes as they occur in uncomplicated rubella the author[4] was impressed by the different degrees of increased capillary fragility and thrombocytopenia, persisting for widely different periods, which occurred in infections of apparently equal severity. Thus in one case considerable thrombocytopenia persisted for over thirty days with only relatively slight changes in capillary fragility, whilst in another the capillary fragility remained strikingly increased for nearly three weeks although the platelet count had returned to normal by the eighth day, and in others only slight changes were observed in either the platelet count or the capillary fragility. These differences appeared to be due to variations in the susceptibility of the patients' tissues and it seems likely that purpura occurring at the height of an infection may well represent an extreme degree of this susceptibility, resulting in such severe capillary damage, and sometimes thrombocytopenia, that haemorrhages develop. This hypothesis explains how one type of infection may give rise to thrombocytopenic or athrombocytopenic purpura, for it is clear that the cells evincing the greater susceptibility to an infection may be either the megakaryocytes and platelets, or the capillary endothelium. If the latter alone is involved, athrombocytopenic purpura will result. If the megakaryocytes and platelets only are involved, there will be no bleeding, for it has already been shown that thrombocytopenia by itself does not cause purpura, but if the megakaryocytes and platelets, and the capillary endothelium are affected, thrombocytopenic purpura will result. The concept that the development of purpura depends on the susceptibility of the patients' tissues also explains the lack of any obvious relationship between the severity of the infection and the incidence of purpura, although these two factors should probably not be considered as entirely separate, for it may well be that a severe infection occurring in a susceptible patient may have a greater tendency to cause purpura than a mild infection occurring in the same patient.

Although the above mentioned hypothesis may explain cases of purpura occurring during the first few days of an infection, it does not explain the occurrence of purpura during convalescence. Increased capillary fragility and thrombocytopenia may persist long after the symptoms of the primary disease have disappeared, but this does not explain why purpura should suddenly develop at this stage. Nothing is known of the factor or factors which precipitate purpura during convalescence from an infection, but the existence of a symptom-free period before the onset of purpura suggests the possibility of an allergic basis for this condition similar perhaps to that to which nephritis following streptococcal infections has been attributed. Indeed, the period of maximal incidence of purpura following scarlet fever coincides with that of post-scarlatinal nephritis; and if it is accepted that in acute nephritis there is a widespread lesion of the capillaries, it seems possible that the two conditions may be closely related, and that the allergic factor which causes acute nephritis may, in another patient, produce purpura. It is suggested that cases of purpura occurring during convalescence from other infections, including those due to viruses, may be explained on similar lines.

PURPURA DUE TO DRUGS

Purpura due to drugs is uncommon but it has been reported in connection with a large number of different substances, particularly sedormid (allyl-isopropyl-acetyl-carbamide),[1, 11, 34, 47, 61, 62, 79, 89, 123, 127, 142, 147, etc.] the arsenobenzol compounds,[59, 60, 131, 183, 185, 210, etc.] combined bismuth and arsenic therapy[17, 83, 100, 116, 122, etc.] and the sulphonamides.[49, 80, 82, 105, 114, 128, 173, 180, 186, etc.] Other drugs which have been reported as causing purpura are bismuth,[26] quinine,[86, 140, 162, 174, 195]

quinidine,[32,39,148,153] gold,[93,95,102,126,144] iodine compounds,[46,47] chrysarobin,[161] phenobarbitone,[10] aleurate (allyl-isopropyl-barbituric acid),[210] nirvanol,[108] sodium salicylate,[167] insulin,[194] tetra-ethyl-ammonium chloride,[90] digitoxin[25] and ergot.[162] Hertzog and Roscher[97] have reported two cases of thrombocytopenic purpura which they considered to be due to colloidal silver although the patients were also receiving arsenobenzol compounds. Thrombocytopenia and granulocytopenia, occurring simultaneously, have been described following treatment with arsenic and bismuth,[17] thiourea,[151] and dinitrophenol.[106] Purpura has also resulted from the inhalation of menthol[99] and has been described following exposure to DDT insecticide,[109] "leg stocking colour" preparations[124] and as a manifestation of hypersensitivity to insect bites.[63] Finally, although it is not included in the subject of this paper, it must be mentioned that purpura may be a symptom of aplastic anaemia occurring in the course of treatment with certain drugs, notably the arsenobenzol compounds[17] and chloramphenicol.[208]

It has already been emphasized that a substance can be proved to have caused an attack of purpura only if its administration, after recovery, produces a further similar attack. In the reports listed above, this was done only in cases of purpura due to sedormid,[1,11,61,62,89,123,127,142,147] arsenobenzol compounds,[59,60,131,185] sulphonamides,[105] quinine,[86,140,174,195] quinidine,[32,39,148,153] iodides,[46] chrysarobin,[161] insulin,[194] digitoxin[25] and menthol.[99] However good the circumstantial evidence, the remaining reports must be regarded as unproved and this must be borne in mind when the findings in these cases are referred to below.

Insistence that the administration of a test dose of the suspected substance after recovery provides the only method of establishing the diagnosis implies that the hypersensitivity, once it has been established, persists for an appreciable time. In general this seems to be true. In a case of thrombocytopenic purpura due to sedormid studied by the author striking evidence of hypersensitivity persists over twelve years after the original attack of purpura, and Maritschek and Markowicz[140] and Sturgis[195] have described patients who developed thrombocytopenic purpura due to quinine, fifteen and twenty-one years, respectively, after their first attacks. The hypersensitivity may not, however, always persist as long as this. Falconer and Schumacher[61] noted a considerable reduction in sensitivity in their patient a year after her attack of sedormid purpura, and Falconer, Epstein and Mills[60] have described a patient who showed a remarkable decrease in sensitivity to neoarsphenamine over a period of four years. In both these cases, however, it was still possible to demonstrate the hypersensitivity. Whether the hypersensitivity, once it has been established, can ever disappear entirely is not known but it seems improbable that this can happen in under several years.

At least three reports have appeared in which it has been claimed that a drug had caused an attack of purpura although the patient did not develop any symptoms when given the drug again,[28,173] or did not develop purpura again until the drug had been given repeatedly for several months.[144] It is clear from what has been said above that in these cases the attacks of purpura probably had some other cause.

Although foods are a recognized cause of the Henoch-Schönlein syndrome, they appear hardly ever to cause true purpura. Weil[206] has described a youth who developed purpura whenever he ate meat, eggs or fish. The author gave no platelet counts but stated that there was thrombocytopenia. The purpura was preceded by urticaria and it seems possible that this may have been an example of the Henoch-Schönlein syndrome. Ancona, Ellenhorn and Falconer[10] have described a case of athrombocytopenic purpura which appeared definitely to be due to eating crab. However, this case may also have been an example of the Henoch-Schönlein syndrome as the purpura was always associated with the development of oedema of the ankles. Urbach and Gotlieb[202] state that they have seen a case of thrombocytopenic purpura due to anchovies but they give no details. Squier and Madison[192] in a widely quoted paper, describe six patients in whom they considered that thrombocytopenic purpura was due to foods. Administration of the suspected foods produced only very slight changes in the platelet counts and apparently failed to produce purpura, although one patient developed epistaxis when given wheat or cocoa. The patients recovered, however, when the suspected foods were excluded from the diet. By far the most convincing report is that of Dutton[53] whose patient developed thrombocytopenic purpura which he thought was due to citrous fruits. After recovery she was given further fruit. On the first occasion

she developed two ecchymoses and the platelet count fell from 240,000 to 100,000/c.mm. and on the second, the patient developed purpura. She subsequently ate no more citrous fruits and remained well.

Clinical Picture. The purpura resulting from drug idiosyncrasy is a true purpura, that is, the haemorrhages occur in the absence of any inflammatory reaction. The clinical picture is identical with that seen in purpura due to infections, and may vary from the appearance of a small number of petechiae in the skin to the severest forms of purpura with extensive haemorrhages into the skin, subcutaneous tissues and internal organs and from the mucous membranes and urinary tract.

The usual story is that the drug has been taken over a period of days, weeks, or sometimes even for several years with no untoward results, and then suddenly, following a single dose, an attack of purpura has ensued. This may develop within a few hours, and seldom appears more than four or five days after the last dose has been taken. The first symptoms are often mild and may be ignored or overlooked by the patient. If the drug is stopped at this stage severe purpura may sometimes be averted, but if the patient continues to take the drug more severe haemorrhages will usually develop. However, this is not always true, and severe and even fatal purpura may result even if the drug is stopped when the first symptoms appear. In cases which are not fatal recovery is rapid and complete once the patient stops taking the drug, and bleeding seldom persists for more than a fortnight.

If the drug, for example a hypnotic, is one which is taken intermittently, there may be a history of a number of haemorrhagic episodes, and although each has been associated with the taking of the drug this relationship will often be found to have been overlooked by the patient.

Once the patient has recovered from his original attack of purpura subsequent administration of the drug will often cause further haemorrhages in a remarkably short time. In a case of hypersensitivity to sedormid described by the author[1] bleeding began only fifteen minutes after the drug was taken by mouth, and administration of sedormid,[147] arsenobenzol compounds[59,60,185] and quinidine[39,153] to patients who had recovered from thrombocytopenic purpura due to these drugs has been observed to cause almost complete disappearance of platelets from the bloodstream in less than an hour. In less sensitive patients, however, the drug takes longer to act, and in very slightly sensitive patients the drug may have to be given in therapeutic doses for up to a week before a significant degree of thrombocytopenia is produced, and it may have to be given for even longer before purpura results.[11]

It was stated above that purpura usually appears a few hours to a few days after the last dose of a drug has been given. It is presumably possible with drugs such as bismuth or gold, which are slowly liberated from the site of injection, that the patient might become sensitized some months after the drug had been given but whilst it was still being liberated. This possibility has recently been discussed by Heilskov,[95] whose patient developed severe thrombocytopenic purpura seven and a half months after the administration of the last dose of sanocrysin. In this case, as in a similar case seen by the author, it was not possible to confirm the diagnosis by giving a test dose of the drug, as the patient died.

It has sometimes been claimed that purpura may follow the first dose of a drug[47,123,147] but such claims are clearly dependent upon the accuracy of the patients' statements. Sensitivity may persist for many years, and the patient may well have forgotten that he has taken the drug before or, alternatively, may never have known that he has taken it. This is particularly likely to be true in the case of drugs like quinine, which are often included in proprietary mixtures. It seems probable that a period of sensitisation is always necessary and that purpura due to a drug never occurs after the first dose.

Purpura due to drug idiosyncrasy appears most commonly to be thrombocytopenic, and in most of the cases referred to above the platelets were very greatly reduced in number. A-thrombocytopenic cases do, however, occur, and just as one infection may give rise to either type, so one drug may, in different individuals, give rise to thrombocytopenic or athrombocytopenic purpura. Thus, cases of athrombocytopenic purpura have been reported following treatment with sedormid,[79] neoarsphenamine,[59] sulphapyridine,[186] gold,[93] combined arsenic and bismuth therapy,[17,100] and quinine,[162] although all these substances have much more frequently been reported as having caused thrombocytopenic purpura. One of the five cases of purpura due to exposure to the insecticide DDT reported by Karpinski[109] appears to have been athrombo-

cytopenic, while the rest had very low platelet counts.

Blood Picture. The blood picture is essentially the same as that already described in purpura due to infection, differing from it only in that the changes normally produced by the infection itself are absent.

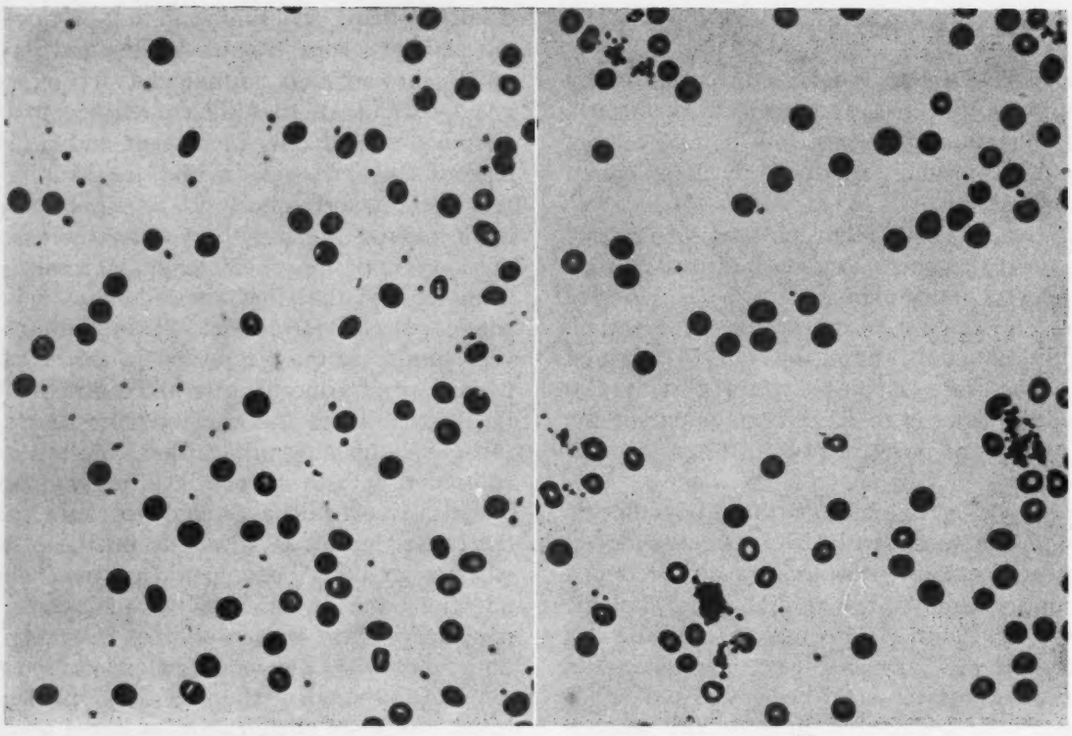
Pathology. Vessels: Highstein and Zeligman[99] have described perivascular infiltration with lymphocytes and monocytes in a case of athrombocytopenic purpura due to menthol. They did not comment on the state of the vessel wall. Apart from this single case report, no abnormalities appear to have been noted in the blood vessels in purpura due to drugs or other chemicals.

Bone marrow: In cases of thrombocytopenic purpura due to sedormid the megakaryocytes have been described as normal,[34,61] reduced in number and showing slight morphologic changes,[89,123] and as showing an inhibition of maturation.[120,147] In cases due to sulphonamides the megakaryocytes have been reported as increased[180] or reduced[128] in number, and as appearing entirely normal,[82] and in purpura due to quinidine, as being reduced in number[39] and as being normal in number and appearance.[32,153] A similarly wide range of findings has been reported in cases of thrombocytopenic purpura due to other drugs. It would seem therefore that morphologic changes in the megakaryocytes have been slight but reports on their numbers have varied considerably. Enumeration of megakaryocytes can be performed satisfactorily only on sections of marrow.[4] Most of these reports were based on sternal puncture material and it is clear that the estimates of the numbers of megakaryocytes were based only on the numbers of these cells aspirated, a figure which varies considerably even in normal marrows. According to Leitner[120] the bone marrow commonly shows a normal or only slightly reduced number of megakaryocytes which have usually appeared normal or have shown only an absence of platelet formation or, less commonly, some inhibition of maturation.

These findings are in rather striking contrast with those seen in thrombocytopenia due to infections, in which gross changes in the megakaryocytes have more commonly been reported. It is shown below that thrombocytopenia due to sedormid, and probably also to other drugs, is due to the action of an antibody which causes platelet lysis in the presence of the drug, the condition being very similar to that produced by antiplatelet serum in animals. Lee and Robertson[119] showed that antiplatelet serum, when given to animals in sufficient dosage to cause purpura, caused only inconstant and probably insignificant changes in the megakaryocytes, and Bedson and Johnston,[24] in similar experiments, found the megakaryocytes increased in number and morphologically normal apart from the fact that they showed no evidence of active platelet formation. These findings are very similar to those reported in thrombocytopenic purpura due to drugs. The differences in the appearances of the megakaryocytes in thrombocytopenic purpura due to infections, as compared with those seen in thrombocytopenic purpura due to drugs, suggest perhaps that in the latter the action is mainly on the platelets whereas in thrombocytopenic purpura due to infections the action may be mainly on the megakaryocytes. It is probable, however, that both megakaryocytes and platelets must be affected, although perhaps to different degrees, in both types of purpura for, as stated above, it is unlikely that any factor could be so specific that it could injure either alone.

Diagnosis. Every patient with purpura should be asked if he has recently taken any drugs, and if he has, it is essential to ensure that he takes no more. The relationship of the drugs to the attack of purpura can only be assessed after recovery.

The author has devised a series of *in vitro* tests which can be used to detect hypersensitivity to sedormid. These are performed by adding sedormid to the patient's blood after the platelet count has returned to normal. The most suitable are the reduction of clot retraction by sedormid, the reduction in the number of free platelets in plasma and the fixation of complement. These are described briefly below, and in detail elsewhere.[1–3,5] It is not known whether these tests, modified by using the appropriate drug in place of sedormid, are applicable to cases of purpura due to other drugs, nor is it known whether they are sufficiently sensitive to replace investigation by giving a test dose of the drug in the mildest cases of sedormid purpura. It would seem reasonable in all cases of purpura which appear to be due to drugs to perform the *in vitro* tests first in the hope that they may detect the more sensitive patients in whom the administration of a test dose might provoke a severe or even dangerous attack of purpura. The test dose



4A 4B

FIG. 4. Agglutination of platelets by sedormid in citrated blood from a sedormid-sensitive patient. Photomicrographs of Leishman-stained blood films taken three minutes after the blood had been mixed with isotonic sodium citrate, or with a saturated solution of sedormid in citrate. A, blood + citrate; no platelet agglutination. B, blood + sedormid in citrate; marked platelet agglutination. Reproduced from *Clin. Sc.*, 8: 269, 1949.

could then be reserved for those patients in whom the *in vitro* tests gave negative results.

The quantity given in the first test dose should be small. The author[1] has produced a mild attack of thrombocytopenic purpura by the administration of as little as 1.4×10^{-6} gm. of sedormid to a highly sensitized patient. Although this is probably quite exceptional, it must be realized that the administration of a large dose to a highly sensitized patient may be extremely dangerous.

After the test dose has been given frequent platelet counts should be performed for several hours; and if no significant fall is observed, the counts should be repeated at less frequent intervals for two or three days. The patient should also be examined daily for minor purpuric eruptions which might otherwise pass unnoticed. If a small dose produces neither thrombocytopenia nor purpura, a larger dose may safely be given in a few days. In this way the dose may be safely increased, either until abnormal signs develop or until therapeutic levels are reached. If thrombocytopenia or purpura have still not developed the drug should be continued for several days before it can be concluded that the patient is not sensitive to the drug.[11]

In cases of athrombocytopenic purpura due to drugs patch testing, as described below, may be tried although this is considerably less sensitive than the *in vitro* tests which are only applicable to thrombocytopenic cases. Apart from this, the diagnosis can be established only by the administration of a test dose of the suspected substance.[59,99]

Treatment. The most important point in treatment is clearly to ensure that the patient stops taking the causative drug and also, since this type of hypersensitivity persists for years, to ensure that he never takes it again. Furthermore, he must never take any chemically related drugs, unless these have been shown by test dosing to be innocuous, for it has been shown, both in connection with the sulphonamides[105] and the arsenobenzol compounds,[59,60] that one member of a group of drugs can cause purpura in a patient whose original attack was due to another member of the same group. This is probably also true of the open chain ureides, for it has been shown[3] that adalin (di-ethyl-

acetyl-carbamide) will cause *in vitro* a reduction in the number of free platelets in the blood of patients who have recovered from sedormid purpura, although this drug has no action on the blood of normal individuals.

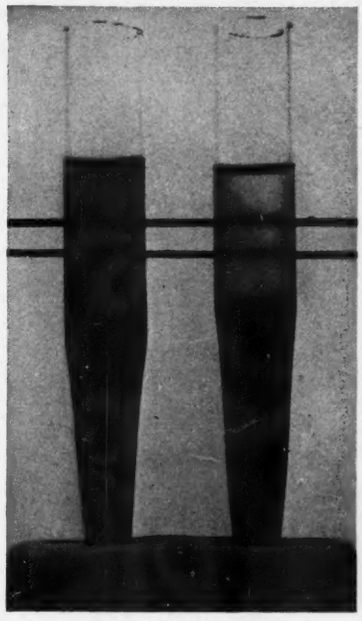
Haemorrhage in purpura due to drugs is often sufficiently severe to necessitate repeated blood transfusions.

In cases of purpura occurring after treatment with heavy metals it would seem rational to use BAL (British Anti-Lewisite), and successful results following its use have been reported in cases of purpura occurring after treatment with gold sodium thiomalate[126] and neoarsphenamine.[183]

Pathogenesis. Thrombocytopenic purpura due to drugs: Thrombocytopenic purpura due to the hypnotic sedormid (allyl-isopropyl-acetyl-carbamide) appears to be the only example of purpura due to a drug which has been subjected to experimental analysis. The following is a summary of the investigations that have been carried out on this subject.[1–3,5]

Action of Sedormid on Platelets in Fluid Blood. Agglutination and lysis of platelets by sedormid in fluid blood: When sedormid is added to the fluid blood of sensitized patients, i.e., patients who have recovered from sedormid purpura, the platelets undergo agglutination and lysis. Sedormid has no action on the blood of controls. Platelet agglutination can be readily demonstrated by making films of blood a few minutes after it has been mixed with a saturated solution of sedormid in isotonic sodium citrate and comparing the appearances of the platelets with those of platelets in blood diluted equally with citrate alone. Figure 4 shows the agglutination of platelets by sedormid in such preparations. The films have been stained with Leishman's stain. If films are made after about half an hour, the platelets will be seen to show signs of lysis. Many will have disappeared and those that remain will not stain normally. Both agglutination and lysis of platelets occur more slowly and to a lesser extent in patients who are only slightly sensitive to sedormid.

Reduction in the number of free platelets in plasma: If the tubes of blood used for the last experiment are allowed to stand and the red and white cells to sediment, the supernatant fluid in the sedormid preparation will appear clear and transparent whereas that in the citrate preparation will be opaque. The very striking difference in the appearances of the two preparations is well shown in Figure 5. The clearing of the plasma in the sedormid preparation is due to platelet agglutination and lysis, the agglutinated platelets having sedimented with the red and white cells.

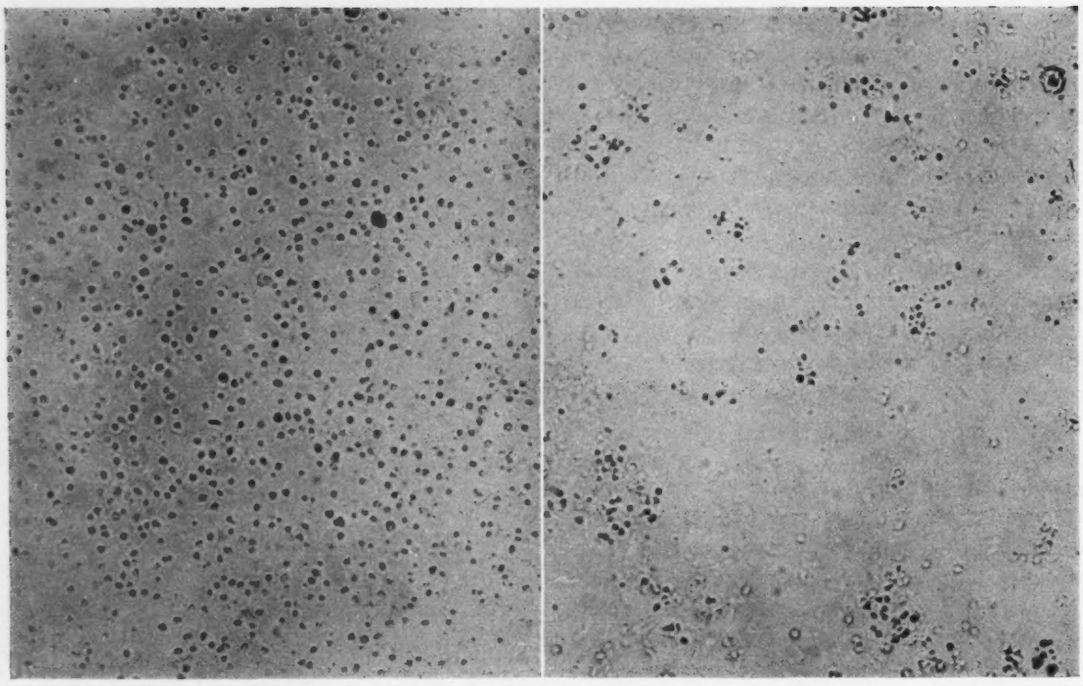


5A 5B

FIG. 5. Clearing of citrated plasma as a result of agglutination and lysis of platelets by sedormid in blood from a sedormid-sensitive patient. The blood has been allowed to stand for five hours before being photographed to permit sedimentation of the red and white cells. A, control preparation containing no sedormid; the supernatant plasma shows normal opalescence and is opaque. B, sedormid preparation; the plasma is clear and transparent. Reproduced from *Clin. Sc.*, 8: 269, 1949.

Agglutination and lysis of platelets by sedormid in plasma: If samples of heparinized plasma are diluted equally with saline, and with a saturated solution of sedormid in saline, and both preparations are immediately placed in haemocytometer chambers, the process of platelet agglutination and lysis can be observed microscopically. The appearances of the platelets in such preparations are shown in Figure 6.

Action of Sedormid on Blood during Coagulation. Lysis of platelets during coagulation: Sedormid causes abnormally rapid lysis of platelets during coagulation. This can be seen if samples of platelet-rich plasma from a sedormid-sensitive patient are taken without anticoagulants and



6A 6B

FIG. 6. Platelet lysis by sedormid in heparinized plasma from a sedormid-sensitive patient. A, plasma + saline; no platelet agglutination or lysis. B, plasma + sedormid in saline; there is considerable platelet lysis. Some platelet "ghosts" can still be seen. Most of the remaining platelets are agglutinated. Reproduced from Progress in Allergy, vol. 3, p. 531, 1952.

are diluted equally with saline or a saturated solution of sedormid in saline, and are then allowed to clot in haemocytometer chambers.

Reduction of clot retraction: The lysis of platelets by sedormid during coagulation results in a striking reduction in clot retraction, for this is dependent upon the presence of an adequate number of normal platelets.[14,129,200] The reduction in clot retraction by sedormid in the blood of a sensitized patient is shown in Figure 7. Sedormid has no action on the clot retraction of the blood of controls.

Complement Fixation by Sedormid. The lysis of platelets by sedormid involves the fixation of complement. This can be demonstrated most readily by diluting blood from a sensitized patient with a saturated solution of sedormid in saline and diluting a further sample equally with saline alone. If the serum obtained from the two preparations after the blood has been allowed to clot is titrated, the complement titre in the sedormid preparation will be found to be much lower than in the saline preparation, thus showing that complement has been fixed. Sedormid does not cause complement fixation in the blood of controls. The complement titres in saline and sedormid in the blood of three sensitized patients and in blood from a series of controls are given in Table II.

Evidence That Platelet Lysis by Sedormid Is Due to the Action of a Factor in the Serum of Sensitized Patients. If platelets isolated from normal blood are suspended in normal sera and in the sera of sedormid-sensitive patients, and the platelets of such patients are suspended in normal sera, and in the sera of sedormid-sensitive patients, and the action of sedormid on the resulting mixtures is observed, it will be found that sedormid causes platelet lysis and complement fixation only in preparations containing serum from sedormid-sensitive patients. In other words, sedormid causes lysis of both normal platelets and those of sedormid-sensitive patients when these are suspended in serum from sensitized patients, but the platelets of sensitized patients are not lysed by sedormid in normal sera. These findings are shown schematically in Figure 8. They show conclusively that the abnormality in the blood of patients who have recovered from sedormid purpura lies in the serum and not in the platelets.

Action of Sedormid on Complement in the Absence of Platelets. Sedormid does not fix complement in the sera of sensitized patients in the absence of

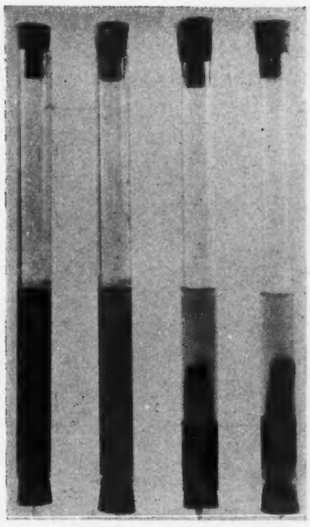
platelets, nor does complement fixation occur if the platelets are replaced by red and white cells.

Action of Sedormid on Platelets in the Absence of Complement. If the serum of a sensitized patient is heated at 56°c. for twenty minutes to destroy its complement, and platelets are then suspended in the complement-free serum, sedormid causes agglutination but no lysis of the platelets. Lysis does occur if further complement is added.

TABLE II
ACTION OF SEDORMID ON COMPLEMENT IN THE BLOOD OF SEDORMID-SENSITIVE PATIENTS AND OF PATIENTS NOT SENSITIVE TO SEDORMID

Patient	Date	Titre of Complement	
		Saline	Sedormid
Sedormid-sensitive Patients			
N. H.	6.1.48	1:15	1:5
	13.1.48	1:15	1:5
	15.6.48	1:12.5	1:5
M. B.	10.1.48	1:15	1:5
	17.1.48	1:15	1:5
	28.5.48	1:17.5	1:10
J. MacP.	23.1.48	1:10	1:5
Patients Not Sensitive to Sedormid			
E. A.		1:15	1:15
N. A.		1:15	1:15
D. G.		1:10	1:10
N. G.		1:15	1:15
F. W.		1:17.5	1:15
N. Gr.		1:10	1:10

Action of Sedormid on the Capillaries. The application of a suspension of sedormid crystals in a saturated solution in propylene-glycol to the skin of some sedormid-sensitive patients causes the appearance of petechial haemorrhages in the area of skin to which the patch is applied. The affected area shows neither hyperaemia nor wheal formation. The skin over the rest of the body shows no change and the platelet count is unaltered. Sedormid has no effect on the skin of controls. The appearance of the skin of a sensitized patient after the application of sedormid for forty-eight hours is shown in Figure 9.



7A 7B

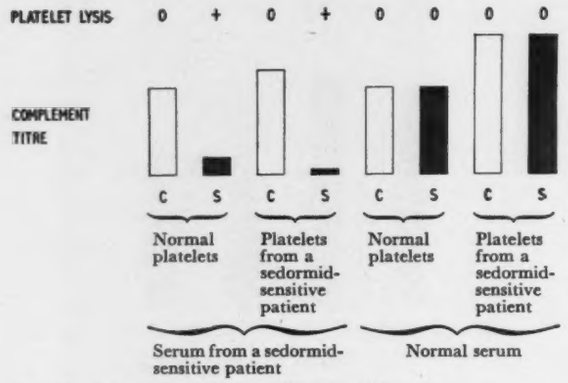
FIG. 7. Action of sedormid on clot retraction of the blood of a sedormid-sensitive patient. A, blood + saturated solution of sedormid in saline; clot retraction negligible. B, blood + saline; clot retraction normal. Reproduced from *Clin. Sc.*, 7: 249, 1949.

Significance of These Findings. These investigations show that sedormid causes platelet lysis in the blood of sensitized patients. This is presumably the cause of the thrombocytopenia in sedormid purpura. Sedormid also causes haemorrhages in the skin of such individuals. These appear to be independent phenomena, for platelet lysis occurs *in vitro*, and the capillary haemorrhages produced by patch testing occur in the absence of thrombocytopenia.

The observations on platelet lysis show that four factors are concerned: platelets, sedormid, complement and the serum of a sensitized patient. Platelet lysis does not occur in the absence of any one of these factors, although platelet agglutination occurs in the absence of complement. No other immune lytic reaction appears to have been described in which more than three participating factors are involved, namely, antigen, antibody and complement. In the lysis of platelets by sedormid it seems probable that the antibody is in the patient's serum. If this is so, it suggests that a union of sedormid with platelets may constitute the antigen, this antigen undergoing lysis in the presence of antibody and complement. This concept readily explains the agglutination of platelets without lysis by sedormid in the ab-

sence of complement, for in all immunologic reactions characterized by agglutination and lysis, agglutination of the antigen occurs in the absence of complement, although complement is necessary for lysis.

As sedormid causes *in vitro* lysis of the platelets



C = Platelet suspension in serum was diluted with saline.
S = Platelet suspension in serum was diluted with a saturate solution of sedormid in saline.

FIG. 8. Platelet lysis and complement fixation by sedormid in suspensions of platelets from a normal patient and a sedormid-sensitive patient in the homologous and the heterologous serum. Reproduced from Progress in Allergy, vol. 3, p. 531, 1952.

of normal individuals, it would seem that this sedormid-platelet antigen must be formed whenever sedormid comes into contact with platelets, and therefore that it is present in the blood stream in all patients taking the drug. That only a minute proportion of these develops purpura can best be explained on the supposition that the union of sedormid with platelets results in a compound of extremely low antigenicity, and that only those patients whose immunity reactions are stimulated by this antigen will manufacture the antibody and so develop thrombocytopenia.

It is clear, therefore, that patients who have recovered from sedormid purpura probably have in their blood stream an anti-platelet antibody which can cause lysis of platelets rendered immunologically antigenic by union with sedormid. The experiments of Bedson summarized above show that anti-platelet serum not only causes platelet lysis but also damages the vascular endothelium. It seems reasonable, therefore, to suppose that the capillary damage in sedormid purpura is due to the action of the antibody which causes platelet lysis, and it may tentatively be suggested that sedormid may combine with the endothelial cells to form a further antigen which then reacts with this antibody, so causing the vascular lesion which plays such an important part in the development of purpura.

Applicability of These Findings to Thrombocytopenic Purpura Due to Other Drugs. It is not known how far these findings are applicable to thrombocytopenic purpura due to other drugs but the observation of Grandjean[86] that the addition of quinine to the blood of a patient who had recovered from thrombocytopenic purpura due to quinine caused a reduction in the number of platelets suggests that the mechanisms underlying sedormid purpura may be similar to those underlying thrombocytopenic purpura due to other drugs.

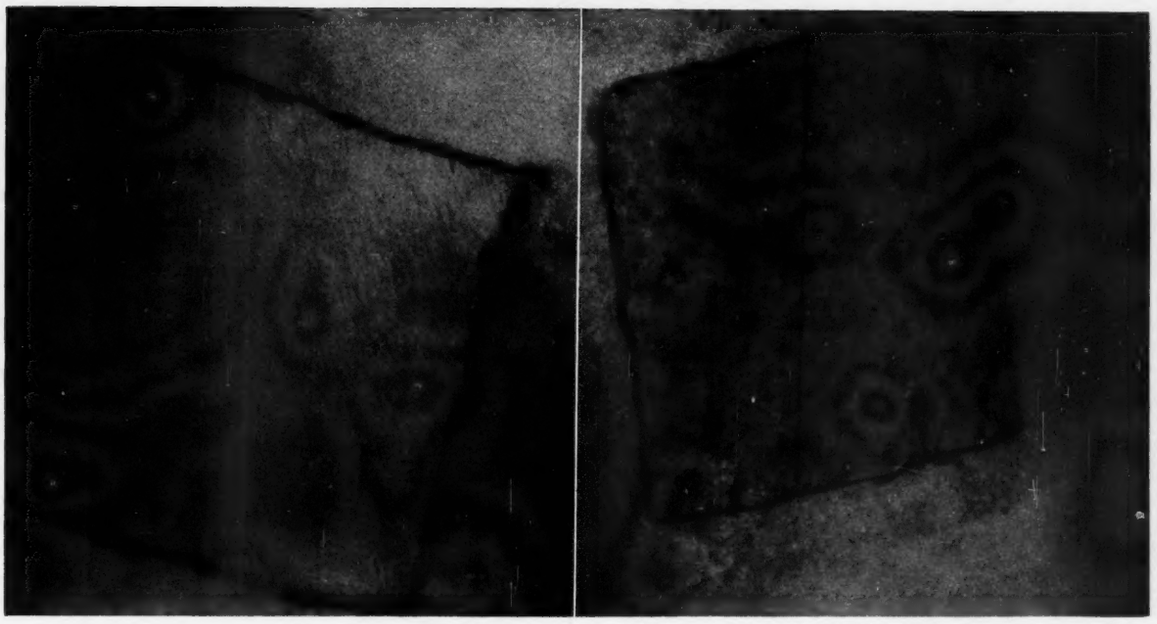
Pathogenesis of Athrombocytopenic Purpura Due to Drugs. That some drugs can cause both thrombocytopenic and athrombocytopenic purpura has already been mentioned. The mechanism by which drugs cause athrombocytopenic purpura is unknown. Since it has been shown that thrombocytopenic purpura due to sedormid, and probably also to other drugs, is caused by an antibody which acts both on the platelets and the capillary endothelium, one can perhaps postulate that athrombocytopenic purpura may be due to an antibody which acts only on the vascular endothelium. Why the platelets should escape the action of the antibody in such cases is not known but it seems possible that in these cases, for some reason, the drug combines with the vascular endothelium and not with the platelets and therefore that only the endothelium can react with the antibody, as it alone becomes antigenic.

SUMMARY

1. Purpura is due to a vascular lesion. Thrombocytopenia, when present, tends to increase the haemorrhagic tendency.

2. Platelets and capillary endothelium are antigenically related. An antibody which injures the platelets can also damage the capillary endothelium. Thrombocytopenia and capillary endothelial damage may, therefore, have a common cause.

3. Allergic purpura is of two types: (1) Purpura associated with an erythematous skin lesion, and also with joint and visceral symptoms: the Henoch-Schönlein syndrome. This syndrome is generally regarded as a manifestation of allergy but, apart from a very small proportion of cases which are undoubtedly due to hypersensitivity to foods, the cause of the



9A 9B

FIG. 9. Result of patch testing a patient who had recovered from sedormid purpura. A, control using propylene glycol alone; the skin in the area of the patch appears normal. B, sedormid in propylene glycol; the skin which has been in contact with sedormid shows numerous closely packed petechial haemorrhages. Reproduced from *Clin. Sc.*, 7: 249, 1949.

syndrome is unknown and its allergic basis is entirely unproved. (2) True purpura in which the surrounding skin is normal. It may be due to an abnormal reaction to an infection or to a drug or, occasionally, to some other substance but is rarely if ever due to foods. Many infections and drugs can cause, in different individuals, both thrombocytopenic and athrombocytopenic purpura.

4. Cases of true purpura due to infections may be divided into those which occur at the height of an infection and those which occur during convalescence. The former type appears to be due to an abnormal susceptibility of the patient's tissues to the factors which normally cause thrombocytopenia and increased capillary fragility at the height of an infection. If this abnormal susceptibility is shown only by the vascular endothelium, athrombocytopenic purpura will result. If the megakaryocytes and platelets are also affected, the purpura will be thrombocytopenic. Purpura occurring during convalescence can best be explained on the assumption of an allergic basis, similar perhaps to that to which nephritis following streptococcal infections has been attributed.

5. The only example of purpura due to a drug which has been subjected to experimental analysis is thrombocytopenic purpura due to sedormid (allyl-isopropyl-acetyl-carbamide). Sedormid appears to act by combining with platelets, so conferring upon them the properties of a weak antigen. This antigen is formed whenever the drug is taken but it has the power of stimulating antibody formation in only a very small proportion of those taking the drug. Thrombocytopenia occurs only in those who develop the antibody and is due to lysis of the platelet-sedormid antigen by antibody and complement. The capillary lesion is probably produced in a similar way, the drug combining with the endothelial cells to form a further antigen which then reacts with the antibody which causes platelet lysis, this reaction producing the vascular lesion which plays such an important part in the development of purpura. It is not known how far these findings are applicable to purpura due to other drugs. An isolated observation on thrombocytopenic purpura due to quinine suggests that the mechanisms underlying sedormid purpura may be similar to those underlying thrombocytopenic purpura due to other drugs. In athrombocytopenic purpura due to drugs it is suggested that only the capillary endothelium combines with the drug to form an antigen, and therefore that it alone reacts with the antibody, this reaction causing the capillary lesion.

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Case Reports

Methamphetamine Intoxication*

W. Gordon Walker, M.D. *and* John Collins Harvey, M.D.

Baltimore, Maryland

The use of benzedrine and related amines, both through prescription and directly by the laity, has increased steadily since the first member of this group was introduced by Prinzmetal[1] for the control of narcolepsy. Despite the warning that cautious and judicious use of the drugs was necessary[2] the practice of using benzedrine and its analogues quite freely is widespread for controlling obesity and as an ancillary measure to dieting in diabetes mellitus and hypertension. The use of these compounds is not without danger for not only have there been reports of fatalities from ingestion of these drugs but there have been many reports in the literature of serious toxic side effects upon several organ systems of the body and in particular upon the central nervous system. The present communication deals with such a case.

CASE REPORT

D. K. (J. H. H., No. 579002), a fifty-four year old previously healthy white female with known diabetes, entered the hospital on July 24, 1951, with progressive disorientation of six hours' duration. Her diabetes has been controlled elsewhere by diet alone for the preceding six years, and two years prior to admission this had been supplemented with a preparation of methamphetamine (D-desoxyephedrine) 2.5 mg. three times daily. Two days before admission she had several loose stools. One day before admission she was found to be mildly febrile. Fever persisted that day and she was put to bed on the morning of the day of admission and left alone for the ensuing eight hours. That evening she was found irrational and quite hyperexcitable by her husband. Admission was arranged.

When the patient was first seen she was acutely ill, lying in bed, muttering to herself and exhibiting prominent and aimless motor activity. Speech was flighty, often unintelligible and at times suggested that the patient was having hallucinations. She was disoriented and unable to give any coherent response or to cooperate during the initial physical examination. The general physical examination revealed little. Temperature was 100.6°F., respirations were 28 per minute, pulse 100 per minute, and the blood pressure was 170/100 mm. Hg. The skin was flushed, warm and moist; there was no rash. Examination of the great organ systems revealed no abnormalities. The neurologic examination was within normal limits except for the previously mentioned disturbance in the sphere of consciousness and a questionable left-sided facial weakness. The hemogram was within normal limits. There was glycosuria. Routine chemical determinations revealed only a moderate hyperglycemia in the fasting state. Cultures of the blood, urine, nasopharynx and feces were not revealing.

Following admission the patient's condition appeared to deteriorate as evidenced by her steadily increasing activity and disorientation. A lumbar puncture was performed with difficulty for the patient struggled throughout the entire procedure. The pressure and dynamics were normal. Examination of the cerebrospinal fluid was normal except for a protein concentration of 87 mg. per cent. Immediately following the procedure the patient went into opisthotonus, had a generalized tonic-clonic convulsion and became deeply comatose. Subsequent neurologic findings were variable and the neurologic status changed rapidly. Initially there was flaccidity on the left side with good tone on the right. The Babinski sign was present bilaterally. She developed searching nystagmus and hippus. The left-sided flaccidity disappeared and the patient exhibited "decorticate rigidity" with the upper extremities held in rigid flexion and the lower extremities extended. Concomitantly she exhibited hyper-

* From the Department of Medicine, Johns Hopkins University and Hospital, Baltimore, Md.

pyrexia with the temperature reaching 105.8°F. The signs of decorticate rigidity were transient and began to disappear after approximately twelve hours. The hypertension subsided and tachycardia disappeared in thirty-six hours. About twenty-four hours following onset of coma she began to respond to painful stimuli and on the evening of the second hospital day she began to respond to verbal stimuli. Subsequently she improved except for persistent personality derangement characterized by inappropriate laughter, wandering conversation and profanity. These changes persisted with very gradual improvement over the succeeding three weeks but it was thought that the patient still exhibited some inappropriate response and abnormally short attention span.

Subsequent to discharge the patient has been well. The diabetes has been easily controlled by diet alone. Drug therapy to control appetite has been abandoned. She has no residual neurologic changes. She has some disturbance of affect as evidenced by short attention span and flight of ideas but the other members of the family maintain that this has been a part of the patient's personality pattern.

Urine collected during the second twenty-four hours of the patient's stay in the hospital was analyzed by Dr. John Herculson, chemist to the Maryland State Racing Commission, and was found to contain methamphetamine (D-desoxyephedrine).* Blood samples drawn at this time revealed none of the drug. It is not clear whether the method is too insensitive to measure accounts in the blood or whether the blood is rapidly cleared of the drug. Examination of the blood in experimentally "doped" horses fails to give positive results when the urine is positive.[3]

* The method used for the identification of the drug was devised by Dr. J. A. Herculson and V. Darpenko, chemists to the Maryland State Racing Commission, and is published with their permission. Identification tests consisted of doing absorption spectra on the acid soluble fraction of a chloroform extract from alkalinized urine. The following procedure was used: (1) Urine was brought to pH of 9.5 with NH_4OH. (2) The sample was extracted three times with 25, 20 and 10 ml. of $CHCl_3$ at 65°C. (3) Extractions (combined) were made acid with HCl and vacuum distilled to dryness over boiling water. One ml. of $CHCl_3$ was added and the residue dissolved in this and transferred to a 15 ml. centrifuge tube. The flask was rinsed with acid water (pH 1) and water added to the centrifuge tube. (4) The tube was shaken vigorously and centrifuged. (5) The acid layer was withdrawn and transferred to another tube. Two ml. of $CHCl_3$ were added and two drops of 1:5 NH_4OH; the tube was shaken and centrifuged. (6) The water layer (which must be alkaline) was drawn off by a pipette and discarded. (7) To the $CHCl_3$ layer in the tube 3.5 ml. of water containing one drop of 0.5 NHCl (pH 2) was added. The tube was shaken vigorously and centrifuged. Absorption of the aqueous layer at 257 millimicrons was measured in the Beckman spectrophotometer.

COMMENTS

The initial picture, a febrile illness with hyperactivity, disorientation and hallucinations, suggested an encephalitis of either infectious or toxic origin. Since results of bacteriologic studies and examinations of the cerebrospinal fluid seemed inconsistent with an infectious process, a search for some toxic agent was made. Questioning of the patient's family revealed that she was taking some type of drug with meals, thought initially to be saccharin but later found to be a proprietary preparation of methamphetamine. The patient had been taking 2.5 mg. three times daily. The amount taken in the time immediately preceding hospitalization is not known but it would appear from a count of the pills remaining in the bottle and the date of the filling of the prescription that she had taken only her regular dose.

Waud studied a volunteer who inhaled fumes from benzedrine (approximately 450 mg.) and described effects consistent with sympathetic stimulation.[4] Toxic manifestations appeared to be mainly an exaggeration of these effects. Isolated case reports of overdosage also describe similar pictures. It is interesting that the dosage level at which toxic manifestations begin to appear varied quite considerably. Burn has shown in cats that methamphetamine inactivates amine oxidase, the enzyme responsible for inactivation of epinephrine.[5] It seems plausible to suggest that the drug taken was sufficient to inactivate enough amine oxidase over a period of time to allow development of autointoxication by epinephrine. The clinical picture which this patient presented suggested that there was excessive stimulation by epinephrine or a similar substance. The rate of recovery might provide an index to the rate of formation of amine oxidase in the brain.

SUMMARY

1. A case of intoxication from methamphetamine (D-desoxyephedrine) is presented. Methamphetamine was isolated from the urine.

2. It is suggested that the clinical picture may be due to autointoxication by epinephrine as a

result of inactivation of amine oxidase in the brain by methamphetamine.

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A Metabolic Study Following Extensive Resection of the Small Intestine for Sarcoma*

HERTA SPENCER, M.D., ISAAC LEWIN, M.D.† *and* DANIEL LASZLO, M.D.
New York, New York

A METABOLIC study is presented on a patient in whom extensive resection of the small intestine was performed for multiple recurrences of an intestinal leiomyosarcoma. This investigation was undertaken in order to study the role of disturbed absorption and utilization of nutrients as one of the probable factors contributing to the complex picture in malignancy. An attempt was made to elucidate the mechanism of derangement of the calcium metabolism reported in cases of extensive small intestinal resection.[1–5]

CASE REPORT

A fifty-six year old white male (M. H. No. 53892) was admitted to this hospital in April, 1951; twelve years prior to admission a leiomyosarcoma of the descending colon was removed. Over a period of eleven years several courses of radiation therapy were given to tumor recurrences at various sites of the intestine. Repeated episodes of subacute intestinal obstruction necessitated an exploratory laparotomy in January, 1951, which disclosed multiple areas of stenosis of the small intestine due to recurrent tumor. Approximately 80 per cent of the small intestine was resected and a jejunocolic anastomosis was established. One month postoperatively the patient developed diarrhea with an average of fifteen to twenty loose bowel movements per day.

Physical examination revealed the patient to be a well nourished man with a body height of 186 cm. and a body weight of 62.5 kg; blood pressure was 120/70. Examination of the head, neck, heart and lungs was normal. The only findings of significance were a deep seated movable mass in the right upper abdomen and an extra-rectal nodular mass, both suggestive of tumor recurrences. The remainder of the physical examination was normal.

Laboratory findings were as follows: Hemoglobin 10.5 gm., red blood count 3,500,000; white blood count 5,000 with normal differential count; urine normal; blood urea nitrogen 10 mg. per cent; creatinine 1.5 mg. per cent; fasting blood sugar 84 mg. per cent; total protein 6.9 gm. per cent; albumin 4.3 gm. per cent; globulin 2.6 gm. per cent; cephalin flocculation test and thymol turbidity were normal; serum calcium 10.9 mg. per cent; phosphorus 2.7 mg. per cent; alkaline phosphatase 4 Bodansky units; gastric analysis: free HCL 15°, total 37°. Stool was negative for occult blood, ova and parasites and for enteric pathogens. A small bowel series showed a jejunotransverse colostomy and some dilatation of the loops of the jejunum. X-ray examination of the skeleton showed no osteoporosis.

The patient was asymptomatic except for the diarrhea which gradually decreased to four or five bowel movements per day by the fifth postoperative month. At this time the metabolic study was started. The patient was observed for four months on the metabolic ward; three months after the completion of this study the patient expired in uremia. There was no evidence of renal insufficiency during the metabolic observation.

The significant postmortem findings were a small tumor recurrence at the jejunocolic

* From the Division of Neoplastic Diseases, Montefiore Hospital, New York, N. Y. This project has been supported in part by a grant from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service, and the Edward S. Abelson Memorial Foundation. Presented at the scientific meetings of the American Association for Cancer Research, New York, April 1952.

† Trainee, National Cancer Institute.

anastomosis, a tumor implant on the serosa of the jejunum and a tumor mass in the pelvis. The descending colon, the original site of the leiomyosarcoma, was free of recurrence. Only 135 cm. of upper jejunum were present. It was dilated to a circumference of 10 cm., the folds were prominent in spite of the dilatation indicating possible anatomic compensatory hypertrophy; however, the microscopic examination did not substantiate this assumption. Chronic pyelonephritis, bilateral hydronephrosis due to compression of both ureters by the pelvic tumor seemed to account for the patient's uremia.

Methods. The metabolic routine was described in a previous publication.[6] The patient received a low calcium diet[7] containing a daily average of 2,173 calories (proteins 72.4 gm., carbohydrates 300 gm., fat 75.8 gm.). The nitrogen, calcium, phosphorus, sodium and potassium content of the food and of the excreta were analyzed and balances of these constituents were determined after each six-day period.

Results. The metabolic data, serum calcium levels and the patient's weight curve are shown in Figure 1. Five months after the resection of the small intestine the study was started and was conducted over sixty-nine days in two phases: a continuous study of fifty-one days and after an interruption of seventy-three days, a second phase covering eighteen days. The weight of the patient fluctuated very little during the metabolic study although it was 3½ kg. higher during the second phase of observation. The patient was asymptomatic except for the diarrhea mentioned before.

Calcium metabolism: The patient was ambulatory; his bony frame was large; the skeletal system was not involved by tumor or osteoporosis clinically and was normal at autopsy. The serum calcium levels were normal during the study. The urinary calcium excretion was subnormal and averaged 11 mg./day. The hypocalcinuria persisted even though 5.6 gm. calcium gluconate (periods 5–6) and 12.5 gm. calcium gluconate and 900 cc. skimmed milk were added to the diet daily (periods 9–11). However, when 5.6 gm. calcium gluconate were infused intravenously for six consecutive days, the urinary calcium excretion rose twenty times to 203 mg./day (period 7). On a low calcium intake of an average of 178 mg./day the fecal calcium exceeded the intake by 136 mg. The calcium balances followed the direction of the intake, i.e., on a low calcium intake the calcium balance was negative and became increasingly positive with increased intake. These changes of the calcium balance are shown in Table 1. Raising the calcium intake by 501 mg./day improved the balance by 458 mg., corresponding to a utilization of 91 per cent of the added calcium. The calcium balance became even more positive by increasing the intake to 2,100 mg./day (by adding 900 cc. of skimmed milk and 12.5 gm. of calcium gluconate to the diet). This increment of 1,917 mg. calcium improved the balance by 776 mg. corresponding to a utilization of 40 per cent which is still within the normal range.[8] The intravenous calcium tolerance test[9] was done on two occasions. The twenty-four-hour urinary calcium excretion following these tests was low, 151 mg. (period 4) and 73 mg. (period 11), respectively.

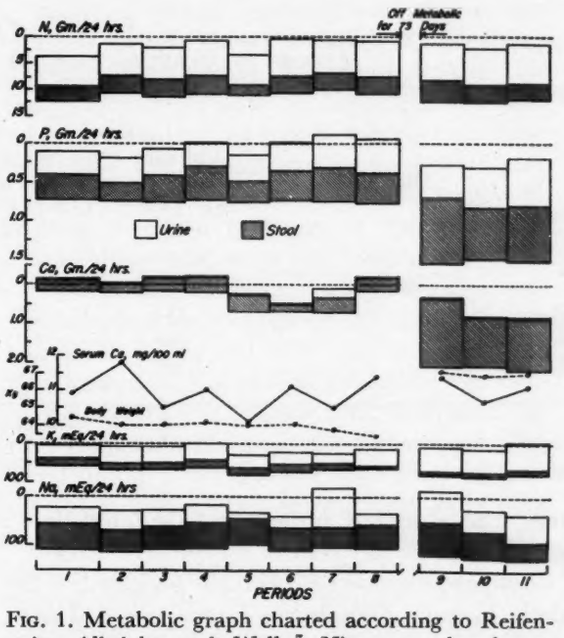


FIG. 1. Metabolic graph charted according to Reifenstein, Albright and Wells.[7] Nitrogen, phosphorus, calcium, potassium and sodium balances; serum calcium levels and weight curve of the patient. The broken horizontal line at zero indicates the equilibrium between *intake* and *output*. *Intake* is charted from the zero line downward; *output* is charted from the *intake* line upward. The shaded areas represent the fecal, the clear areas the urinary excretion. Blank spaces below the zero line represent the positive balance. those above the line negative balances.

Nitrogen metabolism: On an average protein intake of 1.1 gm./kg. body weight/day the average daily urinary nitrogen excretion was 6.5 gm.; the fecal excretion was 3.2 gm. The nitrogen balance was positive throughout the

entire study with an average retention of 1.4 gm./day. The nitrogen balances were in fair agreement with the theoretic balances calculated on the basis of phosphorus, calcium and potassium balances. If the nitrogen lost in the stool is considered to be unabsorbed food protein, the absorbed protein is calculated as 49 gm./day or 68 per cent of the protein intake.

Phosphorus metabolism: During periods 1–8 the daily average phosphorus intake was 742 mg.; during periods 9–11 it was 1,500 mg. On a low phosphorus intake the urinary and fecal phosphorus excretion were about equal; the fecal phosphorus averaged 360 mg./day. On a high phosphorus intake (skimmed milk supplementation) the urinary phosphorus excretion increased only slightly while the fecal phosphorus increased to an average of 723 mg./day. Simultaneously, the daily fecal calcium excretion was 1,437 mg.; the ratio of the fecal Ca/P was 1.98, corresponding to the Ca/P ratio in calcium phosphate.

TABLE I

EFFECT OF VARYING CALCIUM INTAKES UPON CALCIUM BALANCE

Diet	Calcium Intake (mg./24 hr.)	No. of Days of Observation	Balance (mg./24 hr.)	Change of		Utilization* (%)
				Calcium Intake (mg./24 hr.)	Balance (mg./24 hr.)	
Basic	183	27	−128	0	0	..
Diet I	684	12	+330	501	458	91
Diet II	2,100	18	+645	1,917	776	40

$$\text{* Utilization} = \frac{\text{Improvement in balance}}{\text{Increment in intake}} \times 100$$

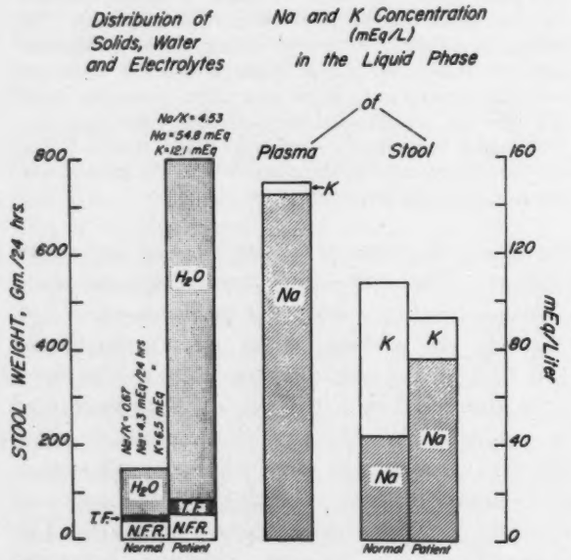


FIG. 2. Stool composition; T.F. = total fat; N. F. R. = non-fat residue; for description see text.

Composition of feces: The composition of feces was studied during the entire metabolic observation. (Fig. 1.) Particular attention was paid to the weight of the stool, its water and fat content during periods 9, 10 and 11. The composition of the stool of the patient and of normals is compared in Figure 2. The weight of the patient's stool was rather constant and averaged 796 gm./day; the water content was 90.3 per cent. The dry weight averaged 80.3 gm./day; of these 27.1 gm. or 35 per cent were fat, corresponding to approximately one third of the fat intake. The fecal sodium and potassium were markedly increased; an average of 54.8 mEq. of sodium and an average of 12.1 mEq. of potassium were excreted in twenty-four hours.

COMMENTS

Metabolic derangements following resection of the small intestine have been reported in experimental animals and in man.[10,14] Removal of a large part of the small intestine was found to be compatible with life. Anatomic compensatory hypertrophy of the remaining small intestine was thought to be responsible for adequate absorption of nutrients.[4,10,13] Flint has shown in great detail that this is the case in experimental animals.[10] However, this was not conclusively proven in man although frequently assumed. Absorption tests and limited metabolic

studies have been previously reported.[1,2,13–18] Prolonged metabolic studies of cases of massive resection of the intestine have not been reported to our knowledge.

Of interest is the influence of a considerably shortened small intestine upon absorption and utilization of nutrients. The present study does not indicate a defect of absorption leading to serious metabolic derangements although an increased loss of fecal fat, water and electrolytes was noted. In spite of the high nitrogen content of the feces the nitrogen balance remained positive. This is in accord with the findings of other investigators.[10,11,13,16–19] The protein anabolism is noteworthy in a patient with a growing neoplasm.[6] Whether the increased fecal nitrogen is due only to unabsorbed food proteins or to nitrogen excreted into the intestinal tract is uncertain and depends, in a given case, on the amount of intestine remaining. Fecal nitrogen has been found to vary directly with the amount of fat in the diet.[10,11,17,19] However, neither the amount nor the type of dietary fat seems to influence the fecal nitrogen significantly.[20] The absorptive capacity of the remaining intestine is best shown by analyzing the calcium metabolism. On a low calcium intake the fecal calcium was higher than the intake; this excess excretion cannot be due to malabsorption alone. In order to clarify the mechanism of this observation the calcium balances were studied under conditions of varied calcium intake. Increasing the calcium intake caused a change from a negative to a positive calcium balance and good utilization of the added intake; the positivity of the balance paralleled the intake increment. The remarkably low urinary calcium excretion in spite of the high calcium intake may indicate an attempt of the organism to conserve calcium in order to meet the calcium requirements and to compensate for calcium losses elsewhere, such as in the stool. This mechanism of compensation is obscure. Persistent hypocalcinuria in spite of adequate calcium intake and normal serum calcium levels may be caused by increased avidity of the skeleton for calcium and/or increased reabsorption of calcium by the renal tubules. The discrepancy between a very low and a twenty times higher urinary calcium excretion when the same amount of calcium was given for six days intravenously, instead of orally, indicates that the hypocalcinuria was not due to a renal component; greater extraction of calcium by the skeletal system is therefore the probable mechanism. This interpretation is in accord with the low urinary calcium excretion following two single calcium tolerance tests[9] which were performed when the patient was on low and on high calcium intake, respectively. The disturbance of calcium metabolism appears to be due to unavoidable losses of calcium in the stool; deficient reabsorption of calcium contained in the large volume of intestinal juices may play a role. The absorption of the dietary calcium *per se* is not impaired and the need for calcium can be met by a higher calcium intake. Low urinary calcium excretions[2,19] and hypocalcemia and tetany have been reported following extensive resection of the small intestine.[1–5] The latter were not noted in our case. In contrast to our experience negative calcium balances were reported on high calcium intake.[16–17]

The analysis of the patient's stool showed that the fecal weight was considerably increased. Its water content amounted to eight times the normal liquid phase of stool. The fecal fat was three times higher than normal and only 64.2 per cent of the ingested fat was "absorbed." The electrolyte concentration in the patient's stool deviated from the normal pattern. Normally, the content of sodium in the stool averages 4.5 mEq./day, of potassium 6.5 mEq./day, the ratio of Na/K is 0.7. In the patient's stool the sodium was twelve times higher than normal (average 54.8 mEq./day), the average potassium was twice the normal value (average 12.1 mEq./day), the ratio of Na/K was 4.5. The serum sodium and potassium levels were normal throughout the entire study. The distribution of electrolytes in plasma and in the liquid phase of the patient's stool showed certain similarities: the fecal sodium content was very high, the sum of sodium and potassium in mEq./L. of liquid phase of the stool approximated the electrolyte concentration of a plasma ultrafiltrate. Similar observations were made in the study of ulcerative colitis.[22] Although the concentration of sodium and potassium (in mEq./L.) in the liquid phase of the stool of the patient and of normals are similar, the ratio of Na/K in the patient is reversed. The analysis of the stool indicates an increased loss of fecal fluid and of electrolytes. The fecal excretion of calcium, phosphorus and fat were previously discussed. Although the fecal excretion of all substances tested was higher than normal, the over-all balances remained normal.

Metabolic aberrations ranging from minimal disturbances to severe nutritional deficiencies incompatible with life have been reported following small intestinal resections. The divergence of these findings may be explained by the factors involved in digestion and absorption. Sufficient amounts of excretory products of the digestive glands stimulated by substances contained in the intestinal juices are needed for digestion. The duration of exposure of food components to the action of digestive enzymes is of importance for proper breakdown prior to absorption. Simple food compounds will be more readily processed than others. Absorption of dietary breakdown products and reabsorption of constituents contained in the intestinal juices may take place at various levels of the intestine. Deficient absorption of nutrients has frequently been reported following the removal of varying portions of the small intestine. However, adequate reabsorption of the excretory products of the digestive glands and of metabolites re-excreted into the intestine following absorption has received little attention. Such impaired reabsorption will lead to a considerable loss of water, electrolytes, minerals and of nitrogenous products. The loss of fat in the stool may partly be due to disturbed absorption although deficient reabsorption of fat excreted into the intestine may constitute a considerable part of the increased fecal fat content.[22] The surface of the remaining intestine available for absorption and for reabsorption may therefore determine the degree of metabolic disturbance. If the absorptive surface is reduced to an extent so that both absorption and reabsorption are impaired, severe nutritional deficiencies will occur.

The analysis of the study of this particular case indicates that the metabolic derangement may be best explained by impaired reabsorption. Failure to demonstrate impairment of absorption in the absence of a large portion of the small intestine indicates that derangements of metabolism in malignancy may be ascribed to factors other than disturbed intestinal absorption.

SUMMARY

1. A metabolic study in a patient with extensive resection of the small intestine due to recurrent leiomyosarcoma is reported.

2. The metabolic data indicate adequate absorption and utilization of nutrients. This is best illustrated by analyzing the calcium balance which improved by increasing the intake. A low urinary calcium excretion irrespective of the calcium intake was noted in the presence of normal serum calcium levels. This is indicative of compensatory efforts of the body to retain calcium. The calcium tolerance test was useful in elucidating this point.

3. The fecal content of water, fat, minerals and electrolytes in the stool was increased. These losses may be due to disturbance of reabsorption of intestinal juices and of metabolites re-excreted into the intestinal canal. The fecal electrolyte content approximated the electrolyte concentration of a plasma ultrafiltrate.

4. The varying degree of metabolic disturbance following intestinal resection appears to depend upon the intestinal surface available for absorption and reabsorption.

5. Derangements of metabolism in cases of malignancy may be ascribed to factors other than impaired intestinal absorption.

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Acute Idiopathic Bulbar Encephalomyelitis*

MAJOR STUART H. WALKER, M.C.
Fort Bliss, Texas

ALTHOUGH idiopathic disseminated encephalomyelitis has been commonly detected in a variety of forms, i.e., a wide range of post-infectious and apparently spontaneous syndromes known as radiculitis, neuronitis, myelitis, encephalitis and meningitis, it has been infrequently recognized as a fulminating bulbar palsy. No evidence for a single etiology of this disease state has been produced. While the viruses of the predisposing disease states have been essentially eliminated as direct agents in the production of the central nervous system damage, no certain proof of the suggested allergic or toxic tissue response to their presence has been obtained either.[1–4] However, these clinical syndromes are related by their common morbid anatomy, chiefly, perivascular demyelination and round cell infiltration, by their common clinical course, a rapid progression of white matter involvement and slow resolution, and their common good prognosis, usually eventual complete recovery because of the paucity of gray matter involvement (except in certain instances such as post-rubeola encephalomyelitis).[5] Because of this usually excellent outcome despite severe and alarming initial manifestations, recognition of these syndromes is essential to insure that every effort will be expended to carry such patients beyond danger into the convalescent phase and to avoid the pessimistic assumption that the irrevocable progression of such apparently malignant processes will lead but to death and permanent disability. Two dramatic examples of idiopathic encephalomyelitis characterized by bulbar palsy, whose rapid and dangerous progression suddenly reversed, illustrate this need for recognition and optimism.

CASE REPORTS

CASE I. R. B., an eleven year old white male, was admitted to the Contagious Division, Cleveland City Hospital, Cleveland, Ohio, on March 1, 1950, with the chief complaint of difficulty in swallowing. Three days prior to admission a slight cough and coryza had developed. The following day he became tired, complained of epigastric pains and occipital headache and vomited several times. On the day prior to admission he became listless, dysphagia appeared and mucus accumulated in the hypopharynx. Although no known poliomyelitis had been present in the community for several months, because of the resultant respiratory embarrassment he was referred to the hospital as a poliomyelitis suspect. Past history revealed nothing contributory. The patient had been hospitalized for pyloroplasty at the age of seven weeks and for tonsillectomy at the age of six years. Except for the premonitory respiratory symptomatology described he had had no illness in the preceding month. There was no family history of neurologic disease.

Physical examination at the time of admission revealed a well-oriented, apprehensive, critically ill child in marked respiratory distress with a temperature of 37.9°C., a heart rate of 88/minute, a respiratory rate of 44/minute and a blood pressure of 120/90 mm. Hg. The pharynx was filled with mucus and harsh gurgling rhonchi were heard throughout the chest. No signs of meningeal irritation were detected. The optic fundi were normal and there was no evidence of enlargement of the skull or separation of the sutures. There was a marked vertical and horizontal nystagmus with the quick phase toward the fixation point, most marked on left lateral gaze. No other abnormalities of the external ocular muscles were detected. The right corneal reflex was absent and the left sluggish. There was weakness of the lower right facial muscles, no gag reflex could be elicited and the uvula deviated to the left. The tongue deviated to the right and could not be pro-

* From the Pediatric and Infectious Disease Section, William Beaumont Army Hospital, Fort Bliss, Tex.

truded beyond the teeth. There was marked hypotonia of the trunk and all extremities with loss of postural control and equally diminished deep reflexes throughout. Incoordination in the finger to nose and heel to knee tests was marked bilaterally. No localized muscle weakness could be distinctly separated from the diffuse hypotonia but it was believed that the proximal muscles of the extremities were most involved. The superficial abdominal and cremasteric reflexes were absent on the left and diminished on the right. The Babinski sign was present bilaterally.

Laboratory examinations at the time of admission revealed normal urine without prophobilinogen, negative serologic tests for syphilis, normal throat flora, hemoglobin 15.0 gm./100 cc.; red blood cells, 4,050,000/cu. mm.; white blood cells, 13,600/cu. mm. with 85 per cent neutrophils, 11 per cent lymphocytes, 4 per cent monocytes and normal platelets. Examination of the spinal fluid revealed it to be under normal pressure and to contain 30 mg./100 cc. total protein, 72 mg./100 cc. sugar, a normal colloidal gold pattern and no cells. Further examinations of the spinal fluid revealed no elevation of pressure but a gradual rise in total protein to the highest level detected, 65 mg./100 cc., three weeks after the onset of the disease state. No tumor cells were detected in the examination of several spinal fluid cell blocks. Radiologic examinations of the skull revealed no abnormality. Examination of acute and convalescent serum specimens for antibodies against the common encephalitic viruses was negative.

The consulting neurologist diagnosed a brain stem glioma, either a fourth ventricular medulloblastoma or an infiltrating pontine spongioblastoma polare.

The patient was treated in the face down, feet elevated position to insure pulmonary drainage and was given constant nursing care to insure suction of all accumulated hypopharyngeal mucus. Increased humidity was produced by a centrifugal humidifier to liquefy pulmonary secretions and oxygen was avoided because of its drying effect. Adequate replacement of fluid, electrolyte, and vitamin expenditures was accomplished by intravenous infusion and nothing was administered by mouth. Sufficient fluid was administered to prevent extracellular depletion and drying of respiratory secretions but the saline intake was strictly curtailed to prevent any increase in cerebral edema. In view of the great dangers from an altered bacterial flora in patients with impaired pulmonary drainage prophylactic antibiotics were avoided. Except for a slight tendency to retention no bladder or bowel disabilities required attention.

Signs of bulbar, ninth, tenth and twelfth nerve involvement rapidly progressed for the first thirty-six hours after hospitalization and a tracheotomy to facilitate pulmonary aeration and drainage was considered at the end of this period. However, as only low grade fever was present and physical and radiologic examination of the lungs showed no massive atelectasis or obstruction, its use was postponed. Neurologic involvement elsewhere showed marked changes during the first two hospital days, spreading and clearing rapidly and concomitantly. Involvement of the right facial nerve partially cleared as paresis of the left (peripheral) became apparent. Cerebellar nystagmus, dysarthria, ataxia in hand and foot movements, and hypotonia increased and pendular knee jerks were detected for the first time. The right Babinski sign disappeared and the right corneal reflex returned while an increase in weakness and pyramidal signs on the left suggested a left hemiparesis. Progression suddenly ceased approximately forty-eight hours after admission and bulbar signs began to recede rapidly. Ninety-six hours after admission all respiratory difficulty had cleared, swallowing of fluids was accomplished without difficulty and peripheral weakness was much improved. Superficial reflexes were normal and signs of pyramidal tract damage had completely cleared twenty-four hours later. Slight paresis of the seventh, ninth, tenth and twelfth nerves was detectable until the seventh hospital day but only a minimal facial palsy persisted thereafter. Deep tendon reflexes in both legs gradually diminished and became absent during this period. Nystagmus and foot and hand incoordination persisted for several weeks while the marked hypotonia and general weakness showed little improvement. Three weeks after admission the patient was able to stand for the first time without support. By this time moderate muscle spasm of neck, back and hamstring muscles was apparent. Low grade fever persisted for the first seven hospital days but was not detected thereafter.

After two weeks of hospital physical therapy the patient was discharged to continue bed rest with passive and active exercises at home. At

this time, four weeks after hospitalization, residual neurologic defects consisted of moderate horizontal nystagmus, slight cerebellar ataxia, slight generalized muscle weakness and hypotonia and slight back muscle spasm. Within two months all signs of neurologic disease except horizontal nystagmus had disappeared completely. One year later he was entirely well except for slight persistent but progressively improving horizontal diplopia and nystagmus.

Case II. R. A., a nineteen year old white male, was admitted to William Beaumont Army Hospital on December 17, 1951, with the chief complaints of severe frontal headache and fever. Three weeks to one week prior to admission he had had a moderate respiratory infection with cough, nasal discharge and malaise but without significant fever or definite localization. Five days prior to admission he developed a mild frontal headache, slight fever, nausea and vomiting. Symptomatology rapidly progressed and for the three days immediately prior to admission he had recurrent chills with high fever, marked vomiting and severe headache. During this period he noted the progressive development of neck stiffness, pain and tenderness in the muscles of his legs, diplopia, numbness of the left side of his face and weakness of the right.

His past history revealed nothing contributory. Neither he nor his family had ever had any neurologic disorders although he had been discharged from the U.S. Navy because of psychologic inadaptability. He had been in contact with no unusual antigens. No encephalitic disease was endemic in his community at this time.

Physical examination at the time of admission revealed a well oriented, alert but apprehensive, slender white adult in slight respiratory distress with a temperature of 103.2°F., a heart rate of 160/minute and a respiratory rate of 28/minute. Mild meningeal irritation was evidenced by slight nuchal rigidity and positive Koenig and Brudzinski signs. There was ptosis of the left eyelid, paralysis of the left lateral rectus muscle, moderate weakness of the entire right side of the face, left hemihypesthesia of the face with a diminished left corneal reflex and dysarthria due to weakness of the tongue bilaterally. There was marked weakness of the anterior neck muscles so that the patient could not lift his head from the bed, and slight variable hypesthesia of the left anterior chest. Generalized hypotonia with inability to sit, slight impairment of hand and foot coordination bilaterally, and horizontal nystagmus with the quick phase back to the fixation point were present. The deep tendon reflexes were generally diminished.

Laboratory examinations revealed normal urine, without porphobilinogens, negative serologic tests for syphilis, normal throat flora, a hemoglobin of 15.4 gm.; red blood cells, 5,090,000; white blood cells, 13,700 with 80 per cent neutrophils (5 stabs), 18 per cent lymphocytes and 2% monocytes. Tuberculin and coccidioidin skin tests were negative and serologic tests on acute and convalescent serum specimens for antibodies against the common encephalitic viruses revealed no reaction. The spinal fluid was under normal pressure but at the time of admission revealed a total protein of 44 mg./100 cc., sugar of 50 mg./100 cc., and a cell count of 70 white blood cells/cu. mm. with 80 per cent lymphocytes. Eighteen days later the total protein had risen to 140 mg./100 cc. and the cell count had dropped to 14/cu. mm. with 80 per cent lymphocytes. A gradual restoration of all factors followed and three months after admission the spinal fluid was entirely normal. No elevation of spinal fluid pressure was ever detected. No tumor cells were detected in the examination of a cell block of the spinal fluid. Radiologic examination of the skull revealed no abnormalities.

The impression of the consulting neurologist was that a brain stem tumor was present, probably a spongioblastoma polare of the pons.

Treatment was essentially as outlined for Case I except for the administration of additional fluids, sodium, chloride and potassium to replace the losses of five days of vomiting and anorexia. Rapid progression of the neurologic involvement continued after admission. On the following day, in addition to the previously noted abnormalities, there was weakness of the jaw particularly on the left, increased sensory loss on the trunk, patchy and bilateral, increased weakness of the anterior neck muscles, increased right-sided incoordination, bilateral Babinski signs, and difficulty in swallowing with an impaired gag reflex and accumulation of hypopharyngeal mucus. He remained alert and lucid and the eyegrounds continued to appear normal. By the third day of hospitalization sensory loss on the face and trunk had diminished, nystagmus was much improved and the ptosis of the left eyelid had disappeared. However, ninth and

tenth nerve involvement increased, the gag reflex disappeared, and distinct respiratory difficulty with a respiratory rate of 40/minutes, slight dusky cyanosis, restlessness and diminished breath sounds at both bases appeared despite the face down, head low position and constant suction. A tracheotomy was considered and preparations made for its use.

However, no further progression occurred and within a few hours respiratory obstruction had definitely receded. Rapid and steadily progressive improvement followed from the third hospital day. By the sixth hospital day the left lateral rectus palsy had disappeared, the right facial weakness had almost cleared, the motor and particularly sensory impairment of the fifth nerve was greatly improved, the tongue was much stronger and the dysphagia and respiratory difficulty had completely cleared. Except for persistent generalized weakness (which was also distinctly improved) all signs of cerebellar involvement had cleared. Some sensory loss over the left anterior trunk was still present but improved. Babinski signs had disappeared and deep tendon reflexes were now completely absent throughout. Slight urinary retention developed into definite urgency and frequency at this time and examination of the urine revealed numerous white cells and hemolytic staphlococcus aureus. Aureomycin cleared all signs of urinary disease within five days and retention did not persist. A gradual decrease in fever was followed by complete afebrility after the eighth hospital day.

Rapid clearing of neurologic disease continued through the third week of hospitalization so that by the end of this period residual disability was limited to moderate weakness of the jaw and right lower face, absent deep reflexes in both legs and generalized slight weakness of all muscles. At this time neck, back and hamstring muscle spasm which had been slight became marked. Six weeks after admission complete muscle evaluation revealed residual weakness of the masseters, right trapezius, gluteals, hip adductors, iliopsoas and hamstrings bilaterally. Minimal spasm of the back and hamstrings persisted. At the time of discharge, fourteen weeks after admission, rest and physiotherapy had achieved complete recovery of all function except for persistent weakness of the upper and middle right trapezius, left hamstring and masseters. Two months thereafter all muscles were normal except for persistent weakness of the masseters, which were still barely able to overcome gravity, and showed definite atrophy.

COMMENTS

The two cases presented clearly demonstrate the characteristic rapidly progressive involvement of white matter, slow resolution of disability and the relatively excellent ultimate outcome of idiopathic disseminated encephalomyelitis. Therapeutic and prognostic considerations require that the diagnosis of this condition be achieved as rapidly as possible. Although the experimental work of Rivers,[1] Morrison[2] and Olitsky[3] has demonstrated the possibility that this pathologic state is due to an antigen-antibody reaction, little progress has been made toward discovering what agent or agents cause the reaction in man. As the pathology of perivascular demyelination and the clinical picture of encephalomyelitis is common to the reaction to many known substances, it is likely that no single etiology will be discovered. This does and will continue to hamper definitive diagnostic technics in this field and indicates the necessity of relying upon clinical characteristics in the distinction of this state. In most instances a clinical diagnosis is possible, usually within a few days of onset.

Toomey and Messina,[5] in a review of seventy-two cases of idiopathic disseminated neuropathy of varying degrees, demonstrated that distinct preceipitating factors were uncommonly detected. In fifty-three of the seventy-two cases no distinct precipitating factor other than a vague upper respiratory infection (in slightly more than 50 per cent of this group) could be detected. Thus although it is known that idiopathic neuronitis or encephalomyelitis may follow many acute bacterial, viral and parasitic infections, exposure to exogenous chemicals, metabolic disturbances including porphyria, avitaminoses and physical injury, in the majority of instances no distinct history of such exposure should be expected. Although in the Toomey and Messina[5] series the age range was from three months to sixty-six years, almost 50 per cent of patients were under twenty years and two-thirds were males. Approximately 15 per cent of these cases showed some ninth cranial nerve involvement with dysphagia and four of the seventy-two developed bronchopneumonia secondary to such respiratory obstruction. Thus bulbar palsy constitutes a distinct and important segment of the encephalomyelitic process.

Although past history, age and sex may be of little value in the individual case, the clinical pattern itself with or without bulbar involvement is usually an acute, rapidly progressive illness often but not necessarily accompanied by fever (in 10 per cent of the cases collected by Toomey and Messina[5]—chiefly neuronitis rather than encephalomyelitis). Despite massive, rapidly extending neurologic disease the patient remains lucid although often apprehensive. There is no evidence of increased intracranial pressure and nuchal rigidity is only occasionally noted (in 10 per cent of cases, according to Toomey and Messina).[5] Progression takes place very rapidly (maximum involvement was apparent within five to seven days in the cases herein reported) and is followed by sudden and rapidly progressive clearing. Motor involvement tends to be scattered and discrete, is usually indicative of lower motor neuronitis and is associated with diminished reflexes and flaccidity. However, pyramidal and cerebellar tract involvement is not uncommon and may obscure the latter pattern. Sensory involvement as noted by Toomey and Messina[5] and in our cases tends to be slight and irregularly distributed. Variability of neurologic findings is characteristic, with complete loss or restoration of function taking place in a twenty-four-hour period. No distinctive alterations in laboratory tests are apparent except for the examination of the spinal fluid which usually contains a few cells (up to 30/cu. mm. in 50 per cent of the series reported by Toomey and Messina) and a normal total protein at the onset but a progressive and characteristic (although certainly not pathognomonic) elevation of protein and disappearance of cells during the following weeks.

With this understanding of the usual clinical pattern, clinical distinction of idiopathic disseminated encephalomyelitis is usually feasible. Occasionally a mild and more slowly progressive case will be confused with multiple sclerosis or, in the adolescent, neuromyelitis optica. As these diseases may actually be related and final diagnosis only possible in retrospect when recurrences of the latter two appear, this distinction may be very difficult. The usual disseminated encephalomyelitis is rapidly progressive, however, and is more likely to be confused with a true infectious encephalitis. Spinal fluid findings ordinarily delineate the mycotic and bacterial encephalitides, such as tuberculous infection, but the viral encephalitides may produce the same spinal fluid alterations in an acute, rapidly progressive, disseminated invasion of the central nervous system. The chief clinical distinction here lies in the lack of gray matter involvement in encephalomyelitis so that the patient remains characteristically lucid and shows little evidence of irritative phenomena, convulsions, muscle spasm, fever and nuchal rigidity. The presence of a distinct and diffuse cerebral edema[6] in true virus encephalitis probably accounts for much of the alteration in sensorium and the lack of cerebral edema in idiopathic disseminated encephalomyelitis[7] probably accounts for the continued lucidity of patients with the latter syndrome.

Therapeutically and prognostically most essential is the distinction of idiopathic disseminated encephalomyelitis from brain stem neoplasm. The clinical findings in each of the reported cases suggested this diagnosis to the consulting neurologists. In retrospect there is no doubt that the almost complete clearing of all neurologic disability and the apparent well being months to years later rules out the possibility of brain stem neoplasm. Yet both the spongioblastoma polare (usually of the pons) and the medulloblastoma (usually originating in the midline of the cerebellum) are not rare in children and young adults and may produce a progressive involvement of cranial nerves and local tracts.[8] Ependymomas (or ependymoblastomas) of the fourth ventricle with local extension into the bulbar and pontine nuclei and neighboring structures may produce a scattered and varying pattern of cranial nerve and spinal tract involvement. Other intracranial neoplasms tend to be well circumscribed and are not likely to be confused with the rapidly progressive and disseminated disease process characteristic of idiopathic encephalomyelitis. Although the spongioblastoma polare is usually slowly progressive, both the medulloblastoma and ependymoma may run their entire course within a few months. However, it is obvious that the only manner in which such lesions could produce progression of the rapidity reported herein is by a pressure effect, through obstruction of the aqueduct or by local hemorrhage. Actual infiltration certainly could not proceed so rapidly. Indeed, most brain stem neoplasms are first detected because of their effect on general intracranial pressure long before local damage becomes apparent, and thus the discovery of normal intracranial pressure in the presence of

rapidly progressive brain stem disease essentially rules out a neoplasm as the cause of the latter.[8] In addition, in encephalomyelitis involvement is usually so widely disseminated (mid-brain, pontine and medullary cranial nerves, peripheral motor and sensory nerves, pyramidal tract and cerebellum) that it cannot be explained by a lesion originating and producing pressure at a single point. Relatively widespread infiltration of the brain stem is characteristic of the spongioblastoma polare but this lesion advances so slowly as to be incompatible with encephalomyelitis and, although the medulloblastoma, the ependymoma and the sarcoma of the leptomeninges are all capable of seeding within the spinal fluid system, their seedings are usually superficial, unaccompanied by signs of underlying parenchymal injury and are productive of increased intracranial pressure. In the cases presented brain stem involvement so dominated the clinical state that widespread dissemination was easily overlooked by the neurologist. In general, the acute illness, occasional fever, marked variability of the neurologic findings and increased cells and protein in the spinal fluid all indicate encephalomyelitis. However, particularly in the presence of local hemorrhage, a neoplasm can present all these findings and reliance should be placed upon the intracranial pressure and the extent of dissemination for final distinction.

An understanding of the pathophysiology and course of idiopathic disseminated encephalomyelitis should ordinarily make possible the diagnosis of its bulbar pattern of involvement and will greatly facilitate the therapy and prognostication of such cases.

SUMMARY

Two cases of acute idiopathic disseminated encephalomyelitis characterized by fulminating bulbar involvement are presented and the clinical distinction of this condition from viral encephalitis and brain stem neoplasm is discussed.

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Paradoxic Embolism*

NOLTON H. BIGELOW, M.D.
Albany, New York

THE passage from the venous into the arterial system of an embolus too large to traverse the pulmonary capillaries constitutes the phenomenon of paradoxic embolism. In most instances a patent foramen ovale has served as the route by which the embolus enters the arterial circulation, although it is theoretically possible that any abnormal opening in either the interauricular or interventricular septum could serve as well.

The nature of the phenomenon of simple embolism, that is, the transportation through the vascular system of particulate matter, was first clearly described by Virchow in 1845.[1] Some years later Rindfleisch[2] postulated that emboli must always go forward in the path of the circulation. He attempted to explain certain apparent inconsistencies, namely, embolization of the arterial circuit originating in a thrombus in the venous circuit, by assuming that small emboli could pass through the pulmonary capillary system. In 1877, however, Cohnheim[3] suggested that a patent foramen ovale could act as a suitable means of by-passing the pulmonary vascular system and four years later Zahn[4] effectively substantiated this hypothesis by demonstrating an embolus lodged in a patent foramen ovale.

Thus within thirty-six years after Virchow's elucidation of the nature of embolism an unequivocal example of paradoxic embolism had been reported. Since that time literally thousands of cases of vascular thrombosis and ordinary embolism have been observed, yet less than forty instances of paradoxic embolism have been recorded. The phenomenon is so rare that doubt is sometimes expressed as to its validity. Even among the reports that have been made, the actual presence of an embolus lodged within the foramen ovale has been recorded in only a few cases.[5,6] Indeed, it is possible that the phenomenon may be overlooked when an embolus is not found entrapped within a patent foramen.

Paradoxic embolism by particulate matter other than portions of vascular thrombi has also been described. On two occasions malignant tumor emboli have been found lodged within the foramen ovale.[7] In several reports it has been suggested that bacteria might be transported from the venous circuit to the arterial through a cardiac shunt rather than through the pulmonary circulation.[8] However, all instances of a microbial type of paradoxic embolism are of dubious validity since in no case has the obvious probability of bacterial passage through the pulmonary circuit been excluded.

The factors necessary for the occurrence of paradoxic embolism are varied, complex and not always readily recognized. The rarity of the phenomenon is more readily comprehensible when the essential criteria are made clear: (1) thrombosis in a venous vascular channel; (2) a patent foramen ovale or interventricular septal defect sufficiently large for an embolus to pass through; (3) reversal of the pressure gradients in the left and right auricles, i.e., the pressure in the right auricle, which is normally less than in the left, must become sufficiently elevated for blood flow to travel from right to left to permit passage of an embolus into the left auricle. Cardiac decompensation and pulmonary embolism are conditions that frequently produce sufficient elevation of right-sided intracardiac blood pressure to produce a right to left auricular pressure gradient; (4) absence of any demonstrable source of embolus formation in the arterial circuit, including pulmonary veins, left atrium, left atrial appendage and left ventricle.

If the aforementioned prerequisites exist, true paradoxic embolism can occur. The recent development of practical clinical cardiac catheterization technics may provide fuller physiologic understanding of the dynamic relationships between cardiac blood flow, septal defects and the transport of emboli through such defects. Furthermore, such technics may provide a

* From the Department of Pathology, Albany Medical College and Albany Hospital, Albany, N. Y.

suitable means of establishing the clinical diagnosis of paradoxic embolism.

Proved cases of paradoxic embolism have, on occasion, been associated with a clear-cut clinical picture. Usually some form of venous thrombosis, such as thrombophlebitis in a lower extremity in a postoperative patient, has developed. An attack of sudden pain in the chest, cyanosis and dyspnea have then followed, together with other evidences of severe pulmonary embolism. Later, in some of these cases, cerebral symptoms such as rapidly developing hemiplegia have supervened, due presumably to occlusion of a cerebral artery by an embolus. Or the appearance of hematuria, often with aching pain and/or localized tenderness in the flank, may be found to be due to infarct in a kidney as a result of embolic occlusion of a renal artery or arteriole. Not infrequently, however, an embolus in the arterial circuit may be associated with no characteristic signs or symptoms whereby its presence can be inferred.

Rarely a patient with the chief signs and symptoms suggestive of paradoxic embolism may recover. Usually, however, another embolus to a lung or a severe degree of cerebral injury terminates the patient's life. Often evidence of paradoxic embolism is first found at postmortem and only in retrospect are a few indicative clinical symptoms or signs of paradoxic embolism uncovered. Thus in the following case there were but few clinical signs or symptoms to indicate the presence of paradoxic embolism.

CASE REPORT

H. Y., a sixty-nine year old white man, was admitted to the hospital because of incapacitating pain in the left flank. Two years previously right nephrectomy had been performed for renal calculi. Clinical evaluation on present admission indicated the presence of a calculus in the left ureter. Ureterolithotomy was performed on the day following admission and a calculus composed of calcium phosphate was removed under spinal anesthesia.

On the seventh postoperative day pain and tenderness were noted in the right calf, with elevation of skin temperature, increase in size of the right calf as compared with the left, but with no tenderness in the femoral triangle. Soreness and muscle spasm of the right calf were elicited by forced dorsiflexion of the foot (Homans' sign). Consequently it was thought that deep thrombophlebitis had developed in the leg.



FIG. 1. Posterior view of heart; an embolus is firmly wedged within the patent foramen oval. The posterior portion of the embolus is clearly seen to be larger than the anterior.

Two hundred mg. of heparin were administered and on the following day the prothrombin time was 32.5 per cent of normal. His temperature, however, remained at about 100°F. On the thirteenth postoperative day he suddenly became pale, sweaty, extremely dyspneic, with a pulse rate of 116 per minute, and died precipitously.

Necropsy revealed the presence of a long, truncated conical embolus, 3.5 cm. in length, extending part way through a patent foramen ovale, which measured 0.7 cm. in greatest dimension. The diameter of the forward end of the embolus in the left auricle was 0.4 cm. while that of the after end was 0.9 cm. Consequently it was solidly wedged in the opening of the foramen. Another embolus completely occluded a secondary branch of the pulmonary artery supplying the base of the upper lobe of the right lung which was the site of a recent infarct that measured 4.0 cm. in greatest dimension. Elsewhere emboli were lodged in several branches of the pulmonary arteries. A recent infarct of the left kidney was also present but no embolus could be demonstrated in any of the renal arteries. (Fig. 1.)

The heart weighed 500 gm., left lung 720 gm., right lung 500 gm. and liver 2,100 gm. In addi-

tion to generalized arteriosclerosis there was chronic passive congestion of the lungs and liver as well as of the other viscera. These findings were interpreted as representing the changes of arteriosclerotic heart disease with congestive heart failure.

COMMENT

In explaining the manner in which paradoxic embolism developed in this case the following sequence of events is believed to have taken place. This elderly man with arteriosclerotic heart disease underwent an operation. Presumably cardiac decompensation occurred during the postoperative period. Thrombophlebitis also developed in the deep veins of the calf of the right leg. An embolus from one of these vessels became lodged in a secondary branch of the pulmonary artery and was present for a sufficiently long period of time for an infarct to occur. Other emboli were discharged into the venous circuit, at least one of which passed through the patent foramen ovale and entered a branch of the left renal artery to produce an infarct in the left kidney. Another long and roughly conical embolus, too large at its base to pass completely through the opening, became caught in the foramen ovale. Subsequent emboli then entered the pulmonary circulation to produce a degree of embolism in those organs sufficiently severe to lead to the patient's death.

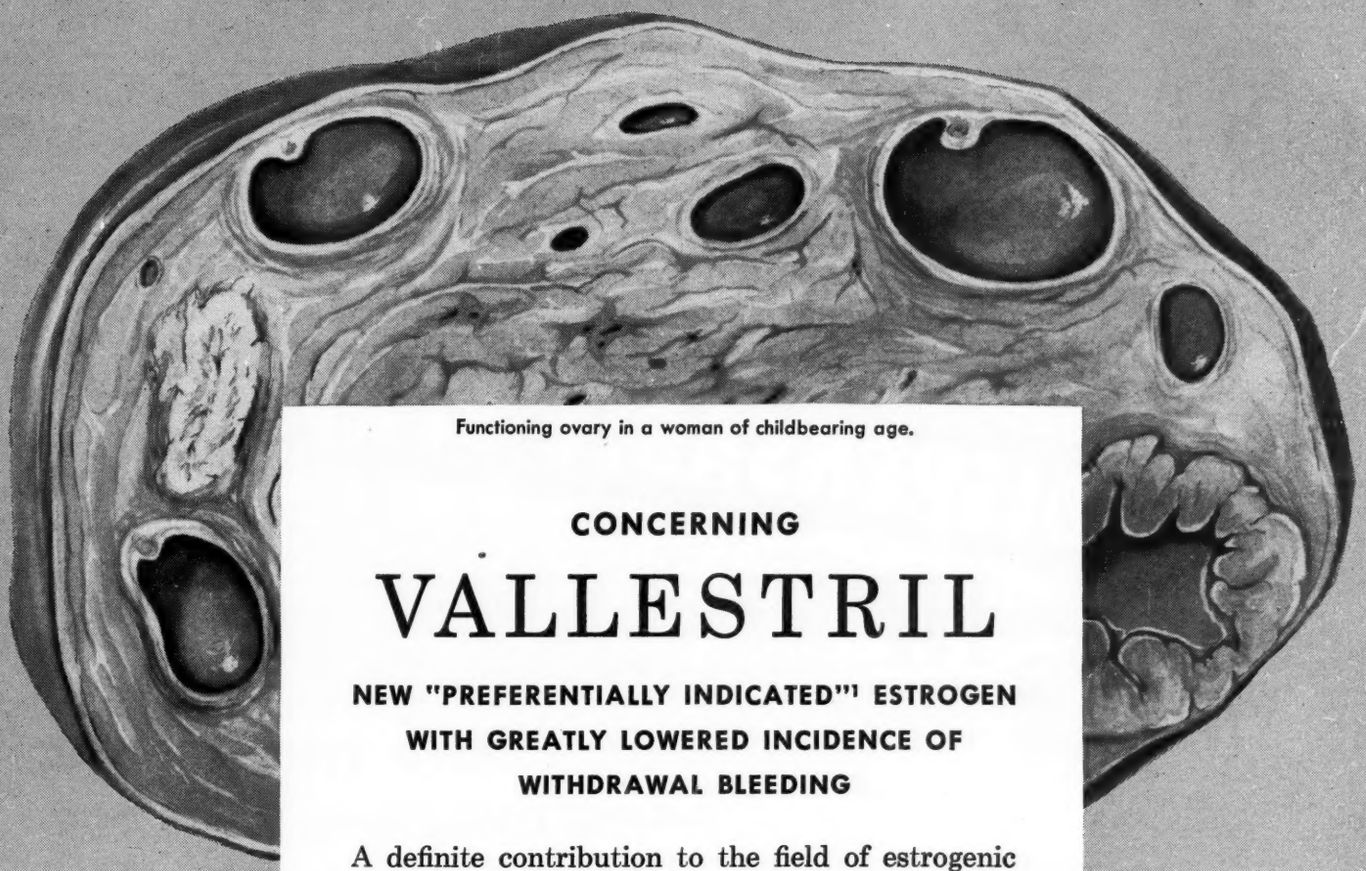
SUMMARY

A case of paradoxic embolism is presented. Although the nature and mechanism of this unusual phenomenon have been recognized for at least seventy-five years, less than forty acceptable instances of thrombotic emboli which have passed through a patent cardiac septal defect have been reported.

A brief résumé of the factors necessary for the occurrence of paradoxic embolism is given.

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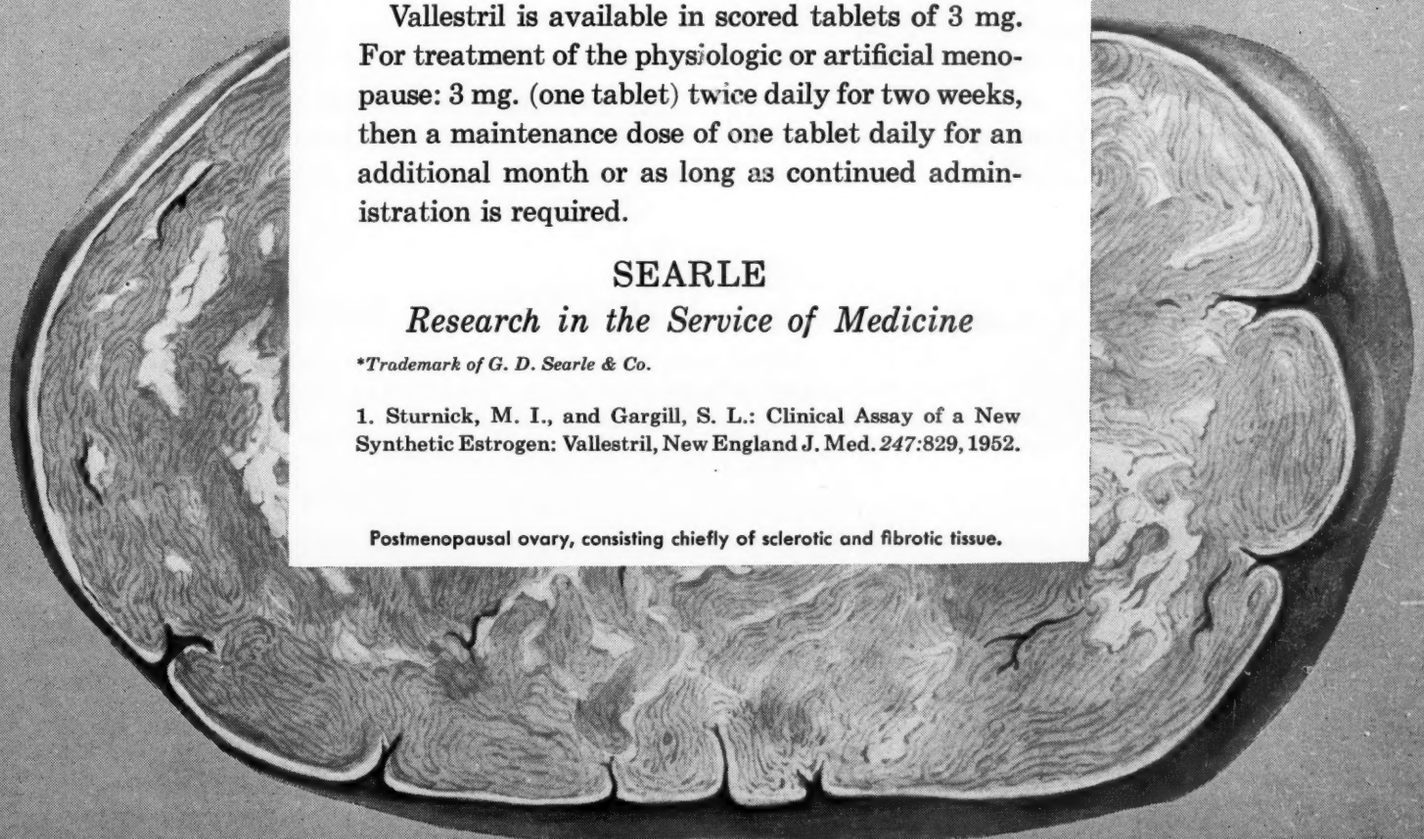
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1. Sturnick, M. I., and Gargill, S. L.: Clinical Assay of a New Synthetic Estrogen: Vallestril, New England J. Med. *247*:829, 1952.



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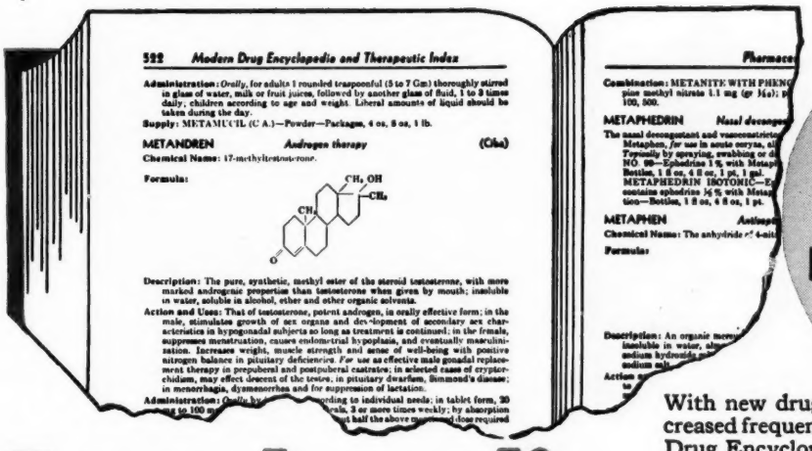
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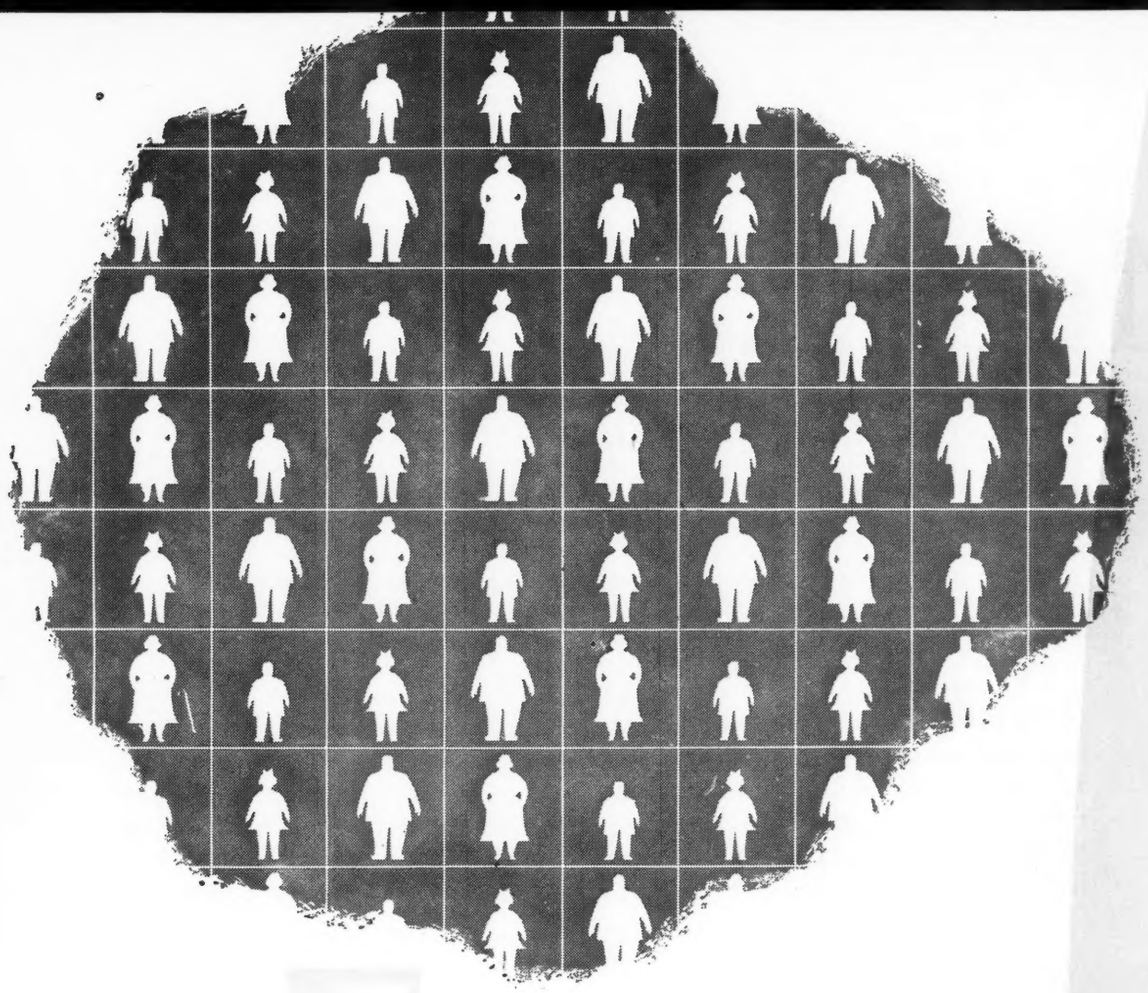
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*Food For Your Heart, a Manual for Patient and Physician, Department of Nutrition, Harvard School of Public Health, Harvard University, The American Heart Association, Inc., New York, 1952. Copies available through local Heart Association.

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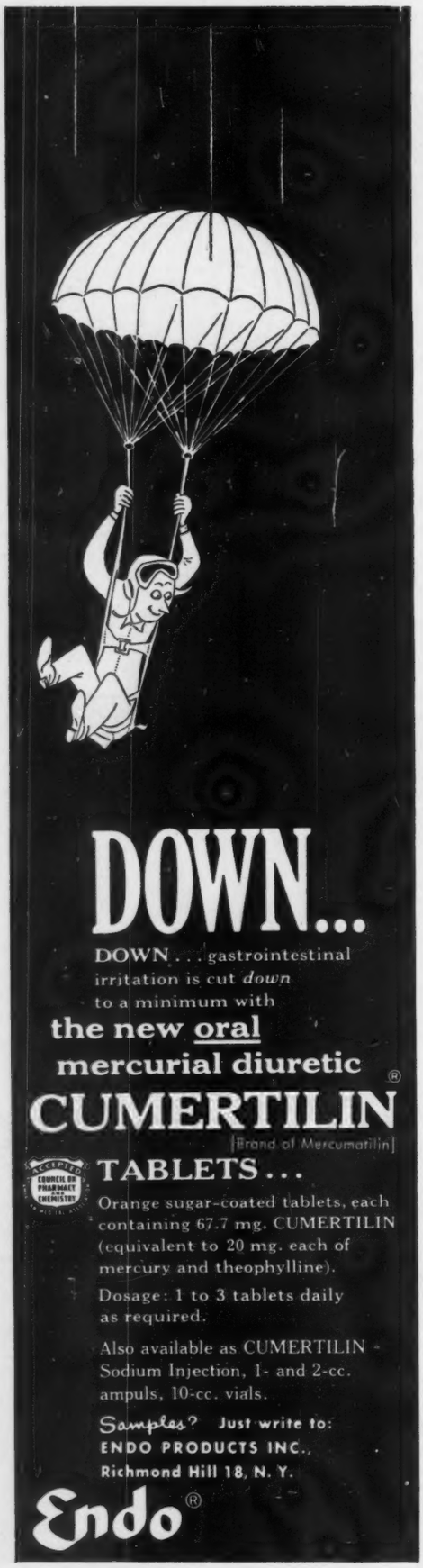
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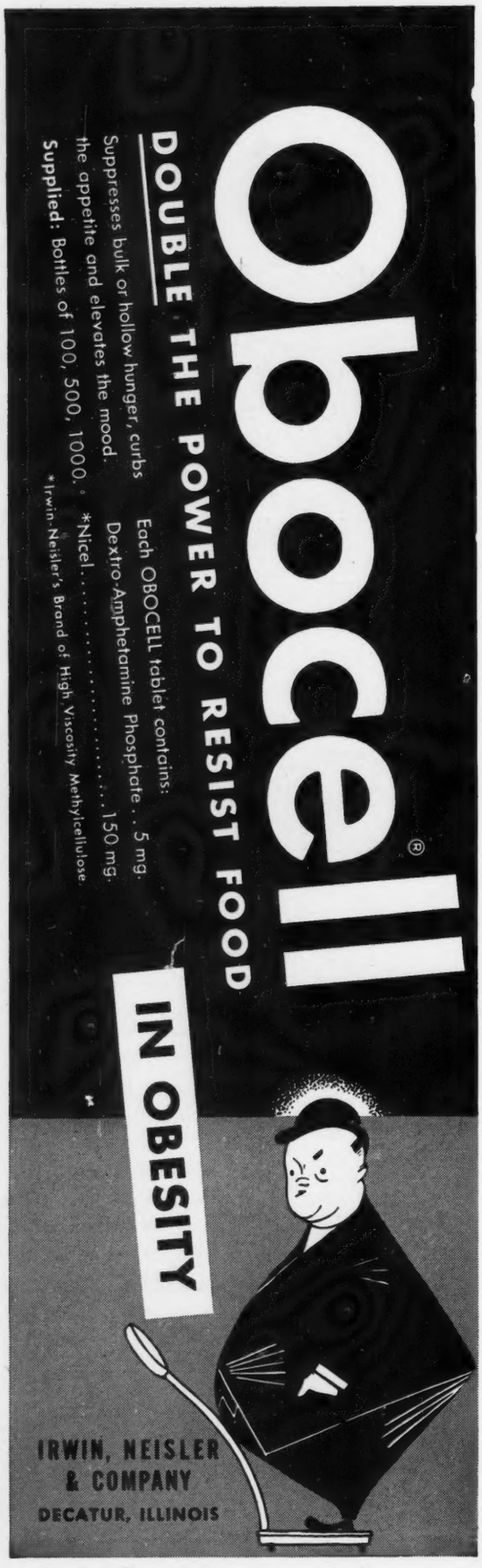
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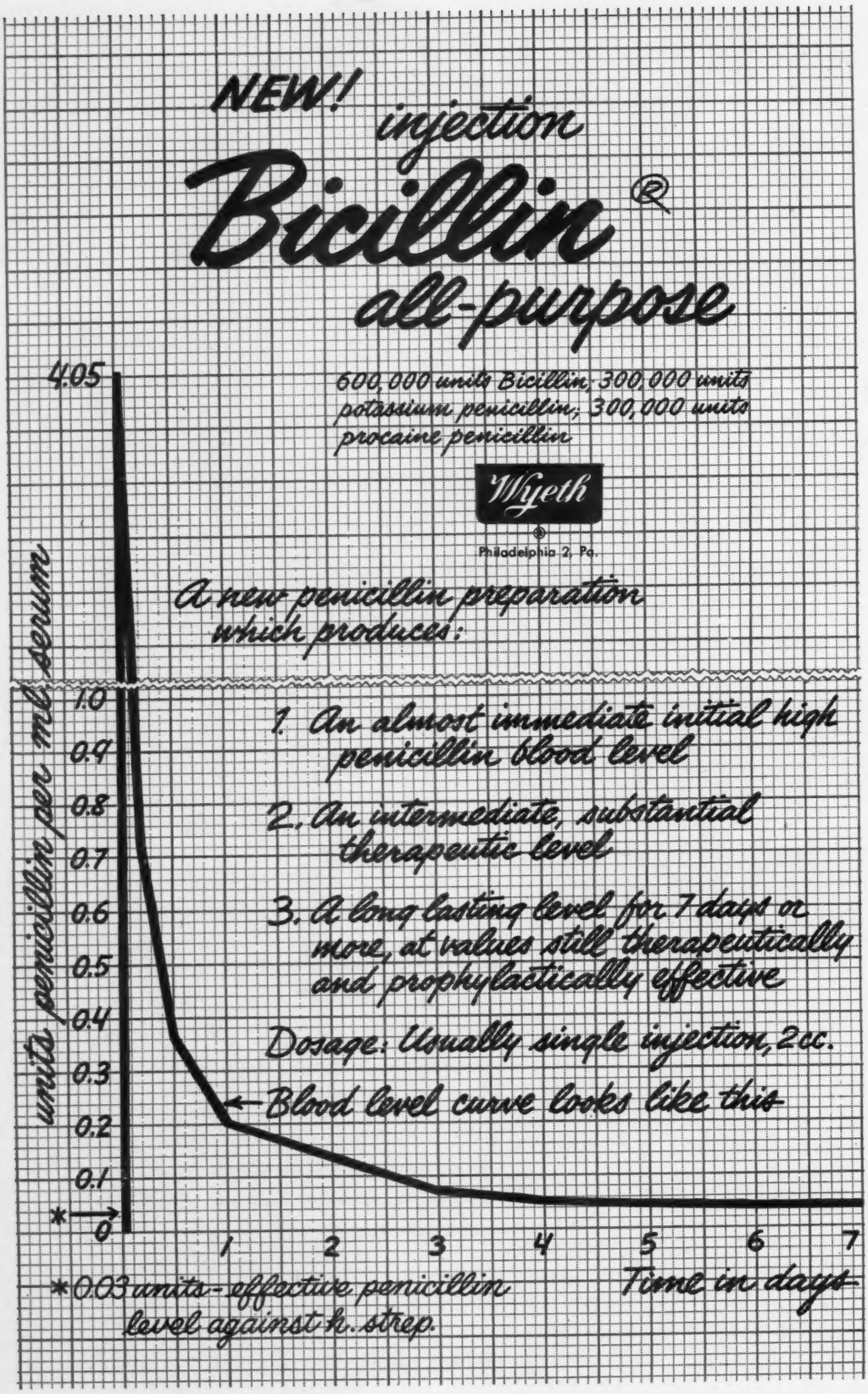
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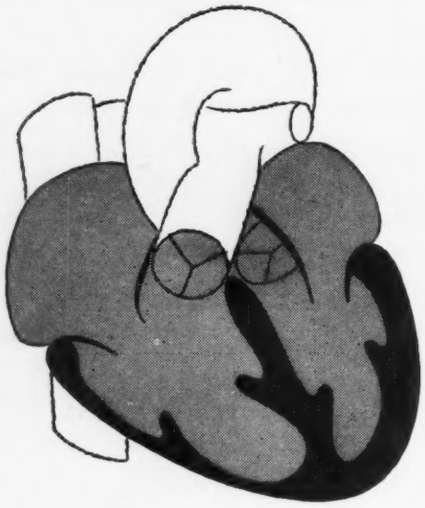
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Unusually palatable. No need to dilute or mask . . . just a pleasantly rich orange flavor, with no aftertaste.

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Each teaspoonful (5 cc.) contains:

Ferric ammonium citrate	200.0 mg.
Vitamin B_{12} U.S.P. (crystalline)	4.0 mcg.
Extractive as obtained from of fresh gastric tissue	450.0 mg.
Folic acid	0.33 mg.
Thiamine HCl (B_1)	1.5 mg.
Riboflavin (B_2)	1.0 mg.
Pyridoxine HCl (B_6)	0.2 mg.

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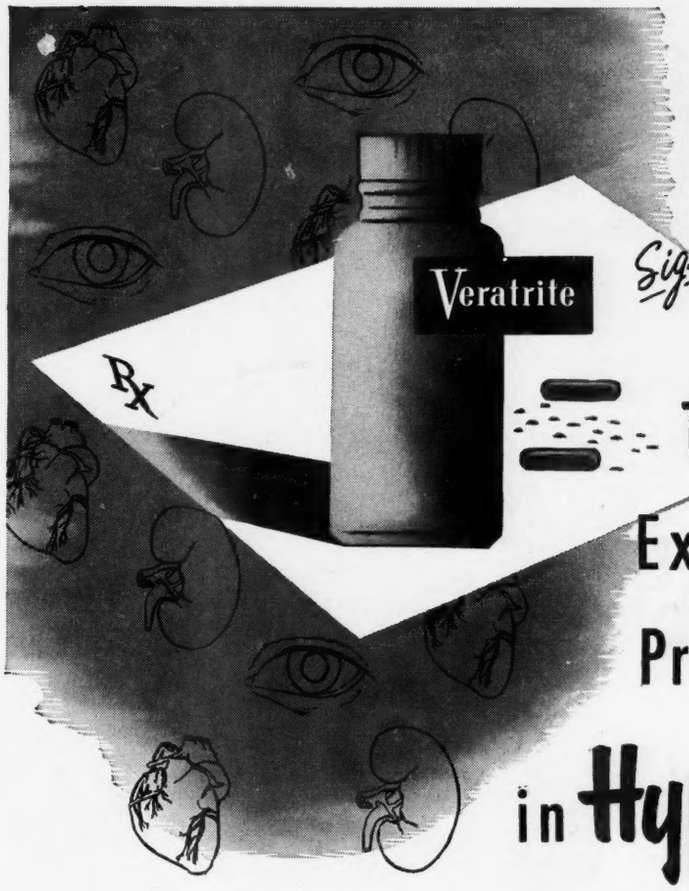
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1. McGuire et al. (1952), J. Antibiotics & Chemo., 2:281, June.
2. Heilman et al. (1952), Proc. Staff Meet. Mayo Clin., 27:385, July 16.
3. Haight and Finland (1952), New Eng. J. Med., 247:227, Aug. 14.

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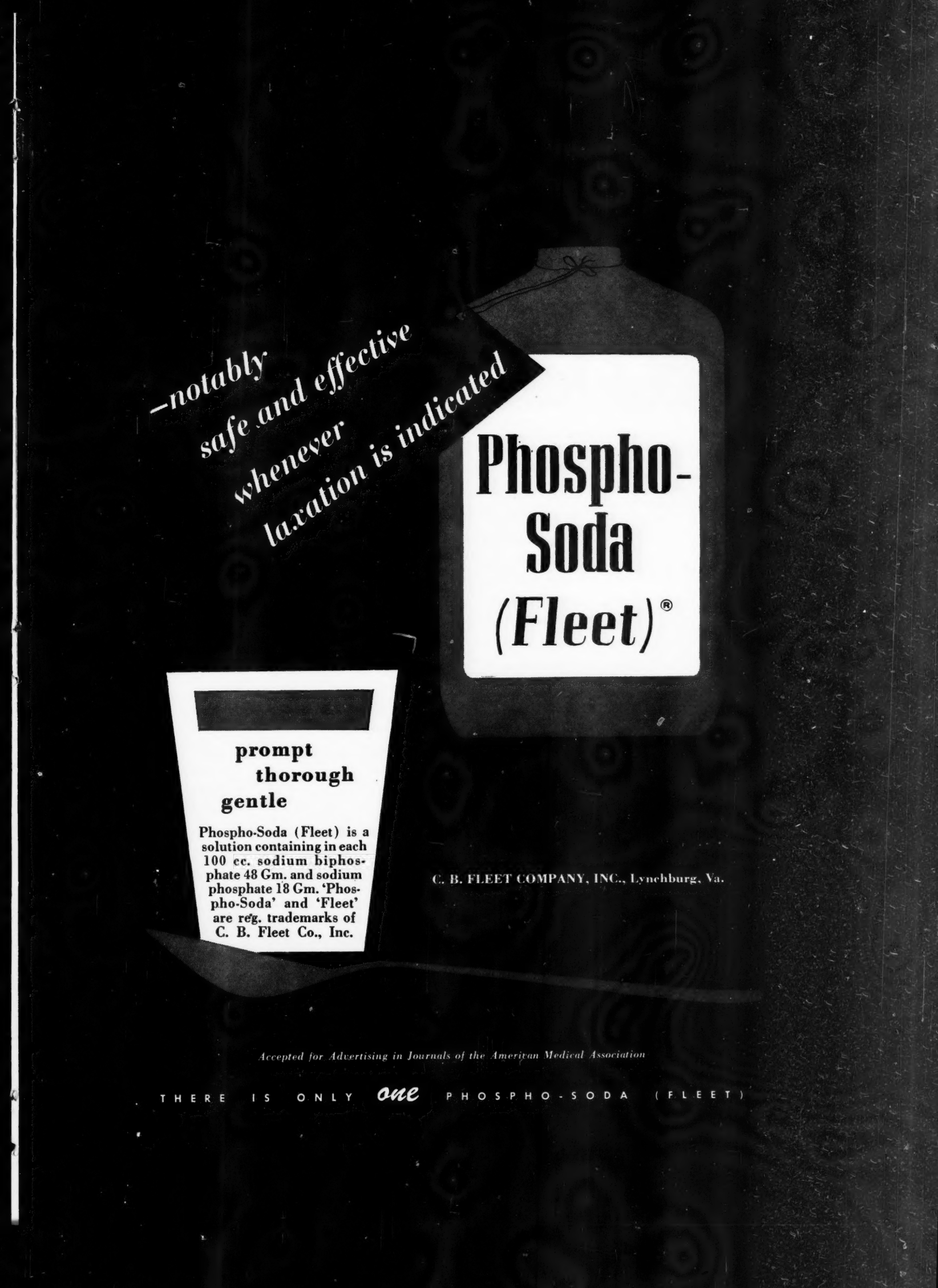
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2. Brown, M. G. and Riseman, J. E. F. JAMA 109: 256, 1937.
3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

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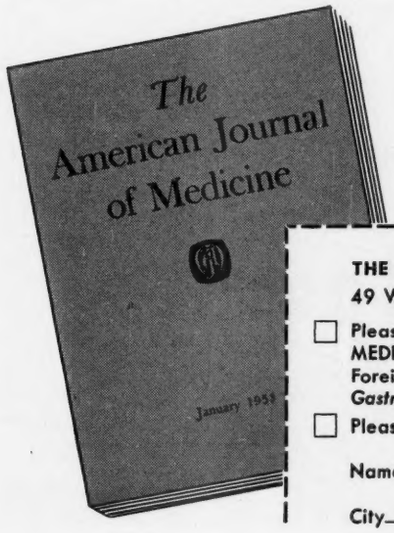
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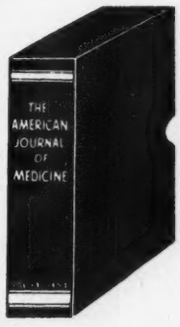
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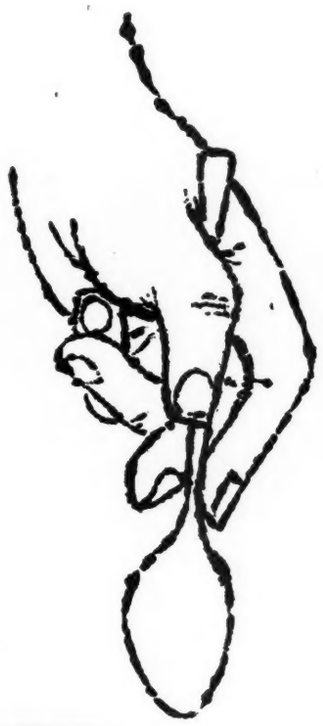
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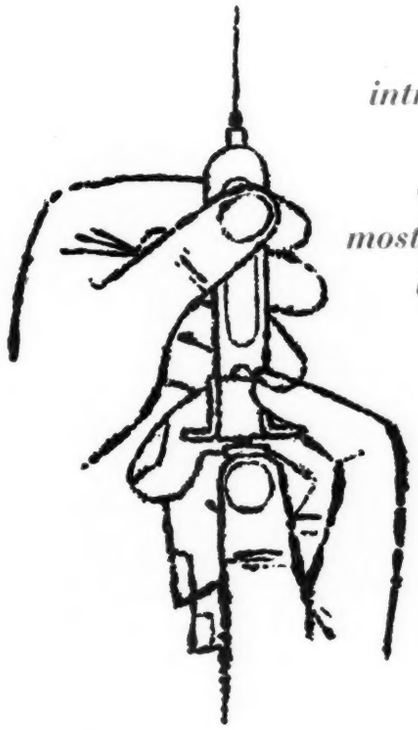
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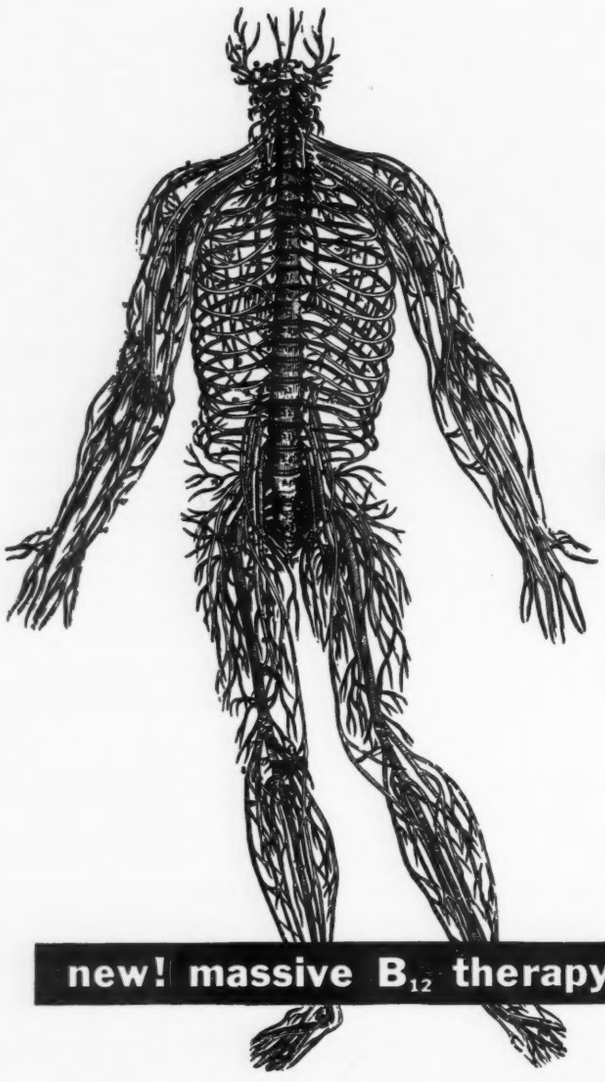
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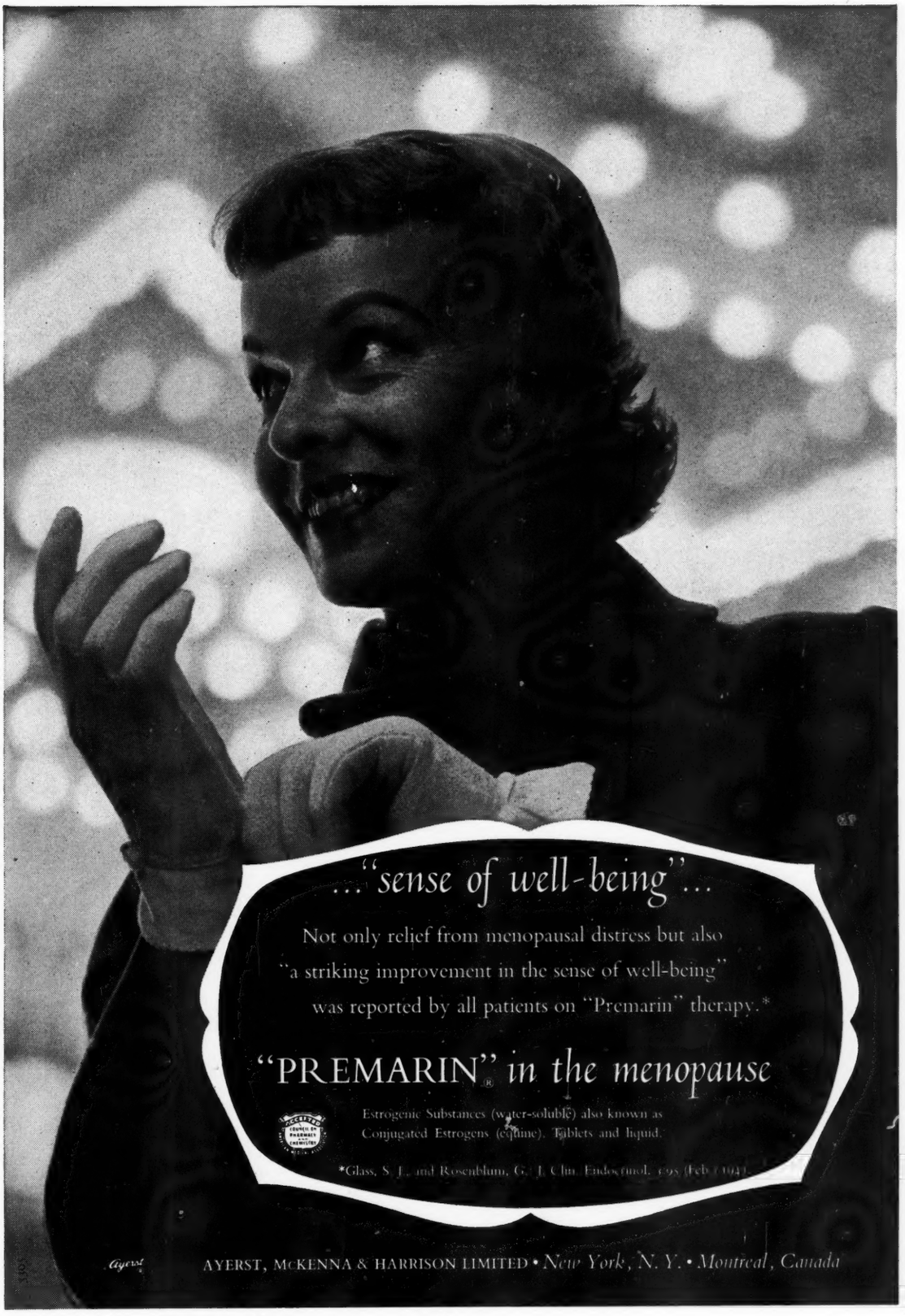
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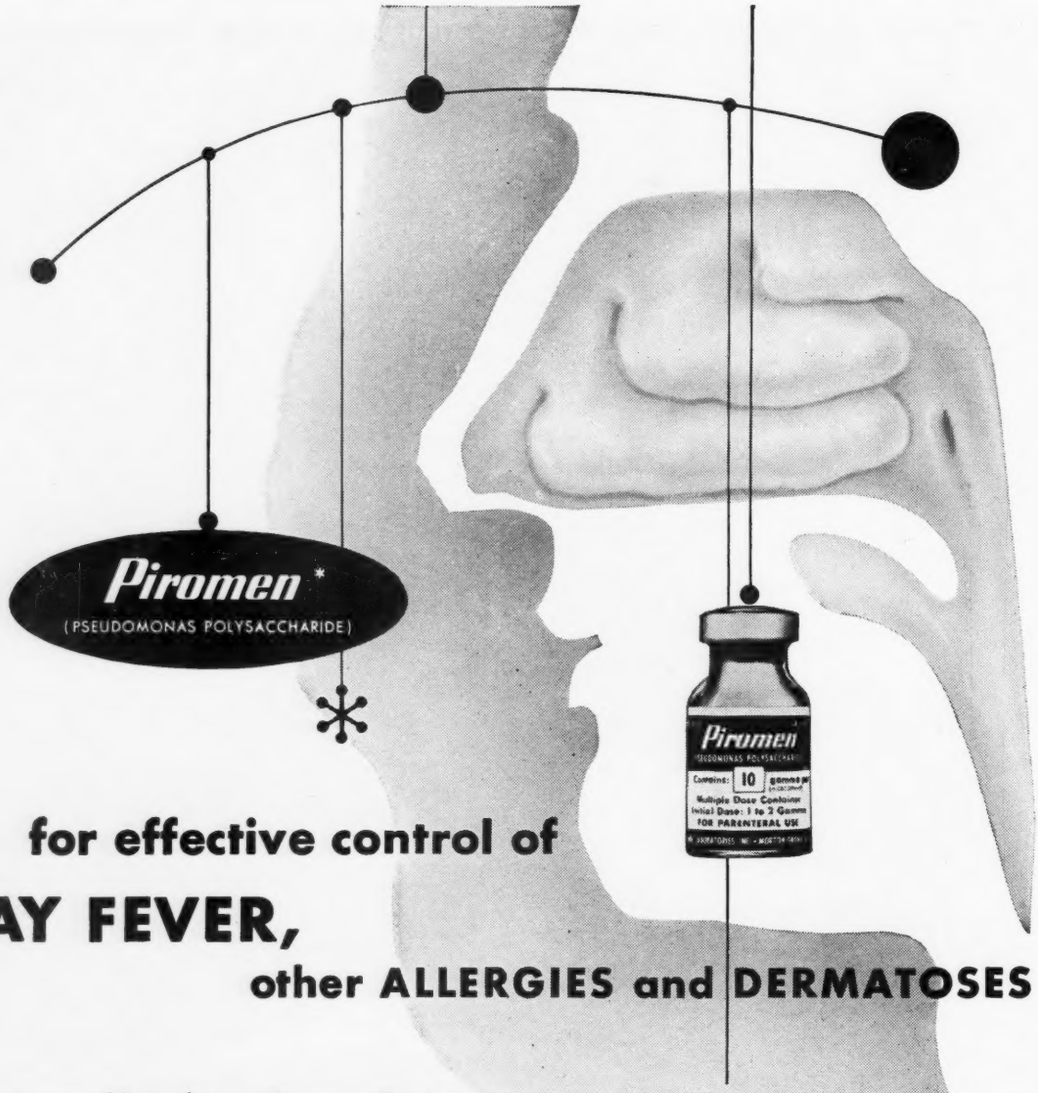
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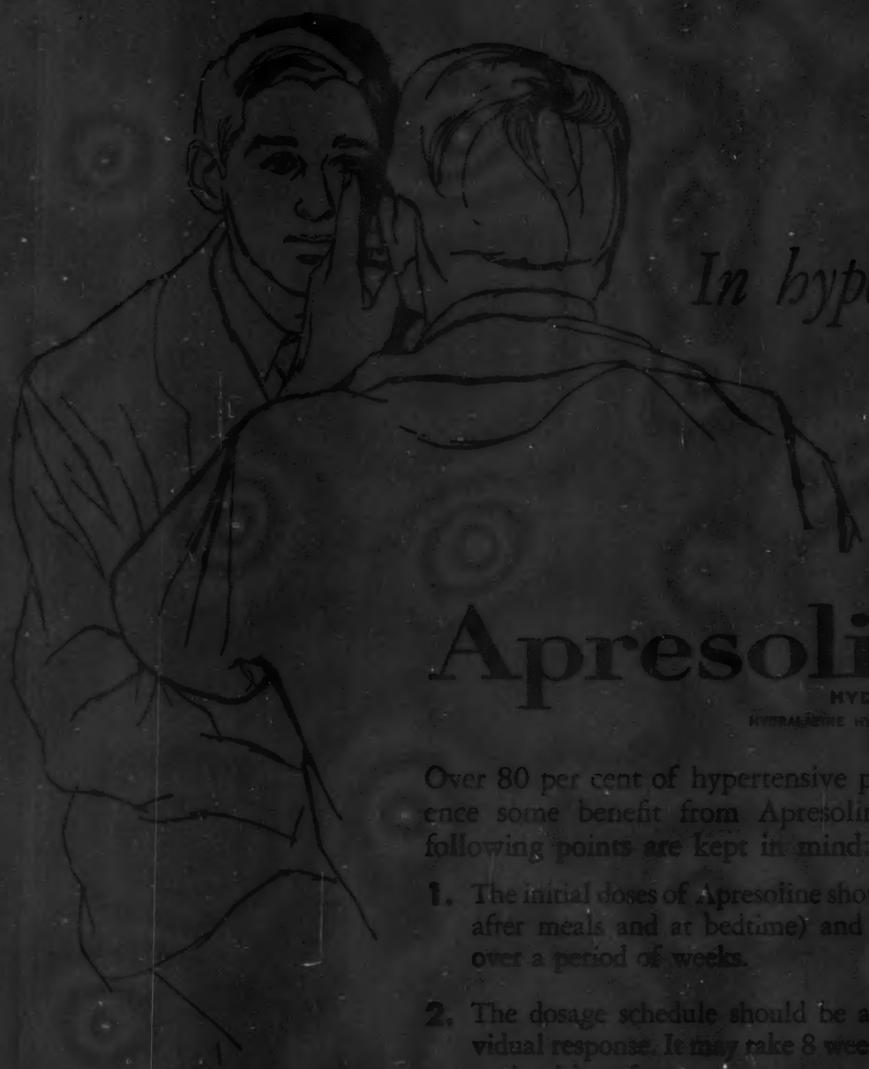
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